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PULMONARY NODULES AND LUNG CANCER

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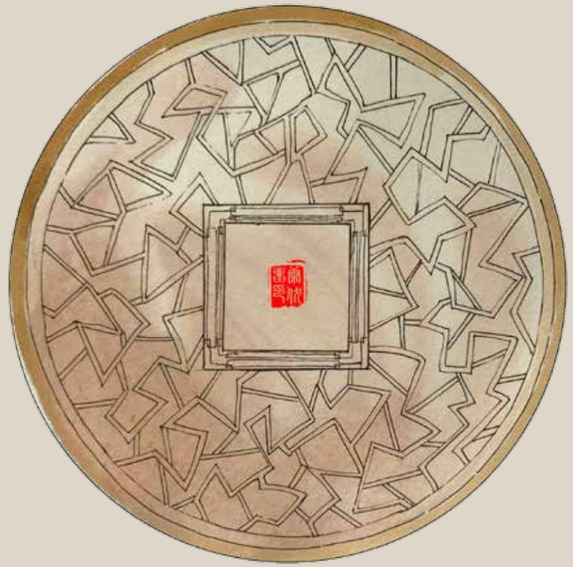
PULMONARY NODULES AND LUNG CANCER

Screening, Diagnosis and Treatment



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Pulmonary Nodules and Lung Cancer
Screening, Diagnosis and Treatment
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We are pleased to announce that the "AME Research Time Medical Book Series" launched by AME Publishing Company have been published as scheduled.

Finishing my medical degree after 4 years and 3 months of study, I decided to quit going on to become a doctor only after 3 months of training. After that, I had been muddling through days and nights until I started engaging in medical academic publishing. Even 10 years after graduation, I had not totally lost the affection for being a doctor. Occasionally, that subconscious feeling would inadvertently arise from the bottom of my heart.

In April 2011, Mr. Tiantian Li, the founder of DXY.cn, and I had a business trip to Philadelphia, where we visited the Mütter Museum. As part of The College of Physicians of Philadelphia, the museum was founded in 1858 and has now become an exhibition hall of various diseases, injuries, deformities, as well as ancient medical instruments and the development of biology. It displays more than 20,000 pieces of items including pictures of wounded bodies at sites of battle, remains of conjoined twins, skeletons of dwarfs, and colons with pathological changes. They even exhibited several exclusive collections such as a soap-like female body and the skull of a two-headed child. This museum is widely known as "BIRTHPLACE OF AMERICAN MEDICINE". Entering an auditorium, we were introduced by the narrator that the inauguration ceremony of the Perelman School of Medicine at the University of Pennsylvania would take place there every year. I asked Mr. Li, "If it was at this auditorium that you had the inauguration ceremony, would you give up being a doctor?" "No," he answered.

In May 2013, we attended a meeting of British Medical Journal (BMJ) and afterwards a gala dinner was held to present awards to a number of outstanding medical teams. The event was hosted annually by the Editor-in-Chief of BMJ and a famous BBC host. Surprisingly, during the award presentation, the speeches made by BMJ never mentioned any high impact papers the teams had published in whichever prestigious journals over the past years. Instead, they laid emphasis on the contributions they had made on improving medical services in certain fields, alleviating the suffering of patients, and reducing the medical expenses.

Many friends of mine wondered what AME means.

AME is an acronym of "Academic Made Easy, Excellent and Enthusiastic". On September 3, 2014, I posted three pictures to social media feeds and asked my friends to select their favourite version of the AME promotional leaflet. Unexpectedly we obtained a perfect translation of "AME" from Dr. Yaxing Shen, Department of Thoracic Surgery, Zhongshan Hospital, Shanghai, who wrote: enjoy a grander sight by devoting to academia (in Chinese, it was adapted from the verse of a famous Chinese poem).

AME is a young company with a pure dream. Whilst having a clear focus on research, we have been adhering to the core value "Patients come first". On April 24, 2014, we developed a public account on WeChat (a popular Chinese social media) and named it "Research Time". With a passion for clinical work, scientific research and the stories of science, "Research Time" disseminates cutting-edge breakthroughs in scientific research, provides moment-to-moment coverage of academic activities and shares rarely known behind-the-scene stories. With global vision, together we keep abreast of the advances in clinical research; together we meet and join our hands at the Research Time. We are committed to continue developing the AME platform to aid in the continual forward development and dissemination of medical science.

It is said that how one tastes wine indicates one's personality. We would say how one reads gives a better insight to it. The "AME Research Time Medical Books Series" brings together clinical work, scientific research and humanism. Like making a fine dinner, we hope to cook the most delicate cuisine with all the great tastes and aromas that everyone will enjoy.

Stephen Wang
Founder & CEO,
AME Publishing Company

Pulmonary nodules are a common diagnostic problem in the daily clinical routine of radiologists, pulmonologists, and oncologists, as well as thoracic surgeons and radiation oncologists. The challenge in the management of pulmonary nodules lies in the necessity to identify the few lung cancers within the vast majority of benign nodules. This diagnostic dilemma is even more pronounced in patients who are undergoing lung cancer screening, which is performed in otherwise healthy heavy smokers with a high risk for lung cancer.

Nodule characteristics, such as size and density, as well as volume doubling time and metabolic activity, are used in combination with clinical and demographic data (age, gender, ethnicity) to predict the probability for malignancy in individual nodules. Nodules with a high risk for malignancy are then either biopsied or resected directly without prior histologic confirmation.

If proven to be lung cancer, the optimal management of these small cancers is still the subject of debate. While some doctors advocate for a lobectomy, others favor sub-lobar resections or stereotactic radiation therapy.

This book provides an in-depth, up-to-date overview of all the different aspects of the management of pulmonary nodules. World-renowned experts in this field have written the chapters in this book. The book focuses on different aspects of lung cancer screening, the management and diagnosis of solid and sub-solid pulmonary nodules, and last, but not least, also on the different treatment strategies of pulmonary nodules.

This comprehensive book provides the different specialists involved in the management of pulmonary nodules with the latest scientific background, and thus, will serve as an indispensable tool for use in clinical practice.

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Preface

Based on the most recent WHO estimate, lung cancer, the leading cause of cancer-related mortality, accounts for approximately 1.69 million deaths worldwide in 2015. Early detection and treatment of pulmonary carcinoma show significant improvement of patients' survival, thus lung cancer screening is of great importance. The incidence of pulmonary nodules (PNs) is increasing as a result of the widespread use of multislice spiral computed tomography and low dose computed tomography (LDCT). Accordingly, the diagnosis and management of large number of indeterminate pulmonary nodules remain a challenge. Our book consists of the following five chapters: (I) lung cancer screening; (II) ground-glass opacity and lung cancer; (III) pulmonary nodules and lung cancer; (IV) pulmonary nodules diagnosis; (V) treatment of pulmonary nodules.

Notwithstanding the encouraging results of the National Lung Screening Trial (NLST), replicating the 20% lower mortality demonstrated by NLST in practice of LDCT lung cancer screening in the real world remains a challenge, considering the risk of radiation, over-diagnosis bias, false positives and cost benefit. Comprehensive understanding of the hurdles and differences should be the first key step. In the meantime, some new issues such as lung cancer probability of incident PNs, potential biomarkers, low-risk individuals in screening have been proposed and investigated.

Ground-glass opacity nodules (GGNs), the subtype of PNs, attract clinical attention since it is demonstrated that GGNs have more possibility of histology of adenocarcinoma. Natural course, follow-up, prediction of growth, surgical resection, etiology, and correlation between radiology and pathology of GGNs have been further discussed in our book.

Except for the conventional examination methods including CT, PET/CT for PNs, several advanced technologies have emerged for acquiring PNs' imaging information adequately. Examples of such include radiomics, a developing field aimed at deriving automated quantitative imaging features from medical images that can predict nodule and tumour behavior non-invasively, dynamic contrast-enhanced CT (DCE-CT) and dual-energy CT (DECT).

The diagnosis of PNs has increasingly relied on minimally invasive tissue sampling techniques, such as transbronchial biopsy, endobronchial ultrasound (EBUS) or endoscopic ultrasound (EUS) needle aspiration, and transthoracic image guided core needle biopsy. Each with their own features, these modalities have been proven invaluable for the rapid and safe acquisition of tissue used for the diagnosis, staging, and molecular testing of PNs.

The management of PNs should begin with estimating the probability of cancer. For patients with a relatively low probability of cancer, regular follow-up with CT is recommended. For those with a high probability or diagnosis of lung cancer, radical surgical resection or radical radiotherapy is considered.

Our book discusses recent advances in the above issues of PNs in order to help clinical physicians have a comprehensive understanding of PNs and make correct decision in practice.

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The clinical literature supporting the benefit of lung cancer screening is robustly growing, most recently resulting in a European statement supporting efforts towards implementation of lung cancer screening (1). Therefore it is timely to package a comprehensive survey of recent international publications addressing issues across the complex spectrum of activities related to the optimal delivery of lung cancer screening services (2). This complements another dedicated focused issue on lung cancer screening, that I had the pleasure of editing with my colleague, Prof W. Rzyman that also contains important relevant screening information (3). For clinicians, the prospect of markedly increasing the cure rate of early detected lung cancer is highly motivating; however, the responsibility of properly attending to the complexity inherent in consistently delivering an optimal screening process is a critical. Fortunately, we have many independent examples of superb screening results (4-6).

As China begins to implement lung cancer screening, at least in centers of excellence, screening professionals have a profoundly important opportunity, to help the vast numbers of Chinese who have accrued significant tobacco-exposure. At the same time, the existing international experience has exposed the degree of difficulty in transitioning from a symptom-detected lung cancer care community to a more public health-oriented CT screening approach. However, even though the approaches are very different, this is an essential transition as the use of low-dose CT screening in asymptomatic high risk populations can more routinely identify early, curable lung cancer. Fortunately, existing best-practice screening approaches are efficient and economically if done correctly (7). In addition, emerging opportunities exist to further optimize the imaging processes to sustain the continuous improvement of the screening process (8,9). Yet, the greatest improvement with improving screening efficiencies will be obtained, as we learn how to better integrate smoking cessation approaches as the smoking rates in China while sharply declining, remain relatively high (10).

Given the vast tobacco consumption in China, the burden of potential premature lung cancer deaths is matched by corresponding potential for premature deaths from tobacco-related coronary artery disease and chronic obstructive lung cancer (8). Both of these major chronic diseases are routinely found in the lung cancer screening CT scans of asymptomatic heavy smokers. Accordingly, large numbers of tobacco-exposed disease will be detected through screening, but the cost implications can be economically managed since the most efficacious interventions, smoking cessation, improving diet, increasing physical activity and statin therapy can be economically implemented across large populations. Therefore the cost and debility of advanced tobacco-related disease can be adaptively preempted in an efficient and socially beneficial fashion. Success in such a remarkable approach will require unprecedented levels of interdisciplinary collaboration. In reading these new publications, it is important to consider such a favorable future state in considering current efforts with lung cancer screening implementation so we can rapidly evolve such that the vast potential health benefits of the early tobacco-related disease management can actually be realized.

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Small pulmonary nodules in baseline and incidence screening rounds of low-dose CT lung cancer screening

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Abstract: Currently, lung cancer screening by low-dose computed tomography (LDCT) is widely recommended for high-risk individuals by US guidelines, but there still is an ongoing debate concerning respective recommendations for European countries. Nevertheless, the available data regarding pulmonary nodules released by lung cancer screening studies could improve future screening guidelines, as well as the clinical practice of incidentally detected pulmonary nodules on routine CT scans. Most lung cancer screening trials present results for baseline and incidence screening rounds separately, clustering pulmonary nodules initially found at baseline screening and newly detected pulmonary nodules after baseline screening together. This approach does not appreciate possible differences among pulmonary nodules detected at baseline and firstly detected at incidence screening rounds and is heavily influenced by methodological differences of the respective screening trials. This review intends to create a basis for assessing non-calcified pulmonary nodules detected during LDCT lung cancer screening in a more clinical relevant manner. The aim is to present data of non-calcified pulmonary baseline nodules and new non-calcified pulmonary incident nodules without clustering them together, thereby also simplifying translation to the clinical practice of incidentally detected pulmonary nodules. Small pulmonary nodules newly detected at incidence screening rounds of LDCT lung cancer screening may possess a greater lung cancer probability than pulmonary baseline nodules at a smaller size, which is essential for the development of new guidelines.

Keywords: Small pulmonary nodules; lung cancer screening; new incident nodules

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Introduction

Lung cancer remains a leading cause of cancer-related death worldwide (1). Various efforts have been made to contain the extent of the disease and an early detection of lung cancer is crucial for successful treatment and prolonged survival (2,3). Lung cancer screening studies using low-dose computed tomography (LDCT) were set up all over the world, to assess the feasibility of detecting lung cancer in high-risk individuals as early as possible (4-6). The National Lung Screening Trial, which is the largest randomized-controlled LDCT lung cancer screening trial, reported a relative reduction in lung cancer-specific mortality of 15%~20% when comparing chest X-ray and LDCT screening (7). Currently, lung cancer screening by LDCT is widely recommended for high-risk individuals by US guidelines (8-15). However, there still is an ongoing debate if screening should be recommended for high-risk individuals in Europe, and further evidence is needed (16). Nevertheless, the vast data on (small) pulmonary nodules provided by the lung cancer screening trials enable further insights into the clinical management of pulmonary nodules and the development of

future screening guidelines.

Most LDCT lung cancer screening trials present results for baseline and incidence screening rounds separately and elaborate reviews of this data were published before (4,5,17,18). Although comparing screening rounds provides valuable information about a trial's lung cancer screening performance in general, this approach does not appreciate the possible differences among nodules firstly detected during baseline and incidence screening rounds and is heavily influenced by the methodological differences of the respective LDCT lung cancer screening trials. For instance, a lung cancer screening trial with an aggressive baseline screening follow-up strategy may report lower cancer rates during incidence screening rounds, than a trial with a less aggressive strategy at baseline screening, even though the overall lung cancer rate is similar. However, only limited evidence concerning the different groups of pulmonary nodules identified is provided. Non-calcified pulmonary nodules detected at baseline screening consist of a combination of nodules that may have been present for years and a fewer number of more recently developed nodules. Non-calcified pulmonary nodules firstly detected during incidence screening may be entirely new (not present on a previous screen), not new (missed on a previous screen), or below the detection threshold of the respective LDCT lung cancer screening trial on the previous screen (hence, these are growing nodules). Unfortunately, lung cancer screening trials present their data concerning lung cancer rates in the various groups of non-calcified pulmonary nodules differently and the definitions of incidence nodules vary widely (4,5,10,16). The recently released British Thoracic Society Guidelines for the Investigation and Management of Pulmonary Nodules addresses this issue by stating that there is little evidence for the management of new incident nodules that appear on follow-up CTs (19).

This review intends to create a basis for assessing non-calcified pulmonary nodules detected during lung cancer screening in a more clinical relevant manner. The aim is to present detection rates of non-calcified pulmonary baseline nodules and non-calcified pulmonary incident nodules not present on a previous scan (thus new) without clustering them together. Furthermore, lung cancer probabilities of non-calcified baseline and new non-calcified incident pulmonary nodules will be assessed, as well as the lung cancer risk for participants with such nodules. As the majority of trials do not explicitly state rates concerning new non-calcified pulmonary incident nodules, only limited evidence is available for this nodule group. This review focusses mainly on the following European lung cancer screening trials: United Kingdom lung screening (UKLS) trial, Italian detection and screening of early lung cancer by novel imaging technology and molecular assays (DANTE) trial, Danish lung cancer screening trial (DLCST), Dutch-Belgian lung cancer screening trial (NELSON), Italian lung study (ITALUNG), German lung cancer screening intervention study (LUSI); American lung cancer screening trials: National lung screening study (NLST), early lung cancer action project (ELCAP), Mayo CT Screening study (Mayo trial), Pittsburg Lung Screening Study (PLuSS); and the international early lung cancer action project (IELCAP) trial.

Pulmonary nodules in baseline screening rounds of LDCT lung cancer screening

Prevalence of non-calcified pulmonary nodules at baseline rounds of LDCT lung cancer screening

The prevalence of pulmonary nodules at baseline rounds of LDCT lung cancer screening depends on the methodology of the respective screening approach, such as the CT protocol or the use of an artificial detection limit. Additionally, a higher prevalence of certain diseases, such as histoplasmosis, may influence the number of detected solitary lung nodules (20). Most European and American trials with no detection limit (PLuSS and Mayo trial) or detection limit of 3 mm or 15 mm^3 (NELSON and UKLS) reported non-calcified pulmonary nodules in between 41%~51% of baseline participants (*Tables 1,2*) (21,24,31,32). However, the ELCAP and DLCST trial, which both did not employ a detection limited, reported lower non-calcified pulmonary nodule rates in participants at baseline [23% (233/1,000) and 22% (447/2,052) respectively] (23,30). These differences could be explained by a plethora of factors, such as differences in methodology, patient population, infectious disease prevalence, etc. For instance, the difference between the Mayo trial [51% (780/1,520) non-calcified pulmonary nodule baseline prevalence] and ELCAP trial [23% (233/1,000) non-calcified pulmonary nodule baseline prevalence] has been attributed to differences in slice thickness during CT detection (5,30,33). Furthermore, the ELCAP trial only reported nodules of participants with less than six nodules, possibly reducing the non-calcified pulmonary nodule baseline prevalence (30).

Strengthening the case for a higher non-calcified pulmonary nodule prevalence at baseline, at least in the

Table 1 Baseline results of selected European low-dose computed tomography lung cancer screening trials

Variables	UKLS (21)	DANTE (4,22)	DLCST (4,23)	NELSON (4,24,25)	ITALUNG (4,26)	LUSI (4,27)
Participants						
Received CT screening	1,994	1,276	2,052	7,557	1,406	2,029
Age, mean [SD]	67 [4]	65 [5]	57 [5]	59 [6]	61 [4]	58 [5]
Pack years, mean [SD]	NA	47 [25]	36 [13]	42 [19]	43 [18]	36 [18]
Nodule detection limit	≥15 mm^3/≥3 mm	None reported	None reported	≥15 mm^3	≥5 mm	≥5 mm
Participants with lung cancer	42/1,994 (2.1%)	28/1,276 (2.2%)	17/2,052 (0.8%)	70/7,557 (0.9%)	20/1,406 (1.4%)	22/2,029 (1.1%)
Participants with NCNs	1,015/1,994 (50.9%)	NA	447/2,052 (21.8%)	3,816/7,557 (50.5%)	426/1,406 (30.3%)	540/2,029 (26.6%)
% with lung cancer	42/1,015 (4.1%)	NA	17/447 (3.8%)	70/3,816 (1.8%)	20/426 (4.7%)	22/540 (4.1%)
% of NCNs being lung cancer	NA	NA	17/560 (3.0%)	74/8,623 (0.9%)	21/639 (3.3%)	NA
Lung cancer						
Stage I	28/42 (66.7%)	16/28 (57.1%)	9/17 (53.0%)	48/74 (64.9%)	10/21 (47.6%)	18/22 (81.8%)
Histology						
Adenocarcinoma†	25/42 (59.5%)	17/28 (60.7%)	12/17 (70.6%)	37/74 (50.0%)	10/21 (47.6%)	15/22 (68.2%)
Squamous-cell carcinoma	12/42 (28.6%)	8/28 (28.6%)	2/17 (11.8%)	15/74 (20.3%)	6/20 (30.0%)	3/22 (13.6%)
Small-cell Lung cancer	3/42 (7.1%)	2/28 (7.1%)	0	1/74 (1.4%)	1/21 (4.7%)	1/22 (4.5%)
Others	2/42 (4.8%)	1/28 (3.6%)	3/17 (17.6%)	21/74 (28.4%)	4/21 (19.0%)	3/22 (13.6%)

†, bronchioloalveolar carcinomas are considered adenocarcinomas. UKLS, United Kingdom lung screening trial; DANTE, detection and screening of early lung cancer by novel imaging technology and molecular assays; DLCST, Danish lung cancer screening trial; NELSON, Dutch-Belgian lung cancer screening trial; ITALUNG, Italian lung study; LUSI, German lung cancer screening intervention study; SD, standard deviation; NCNs, non-calcified pulmonary nodules; NA, not available.

European smoker or former smoker population, are the recently released results of the UKLS trial's baseline round. This trial shared an analogous methodology with the NELSON trial and confirmed a non-calcified pulmonary nodule baseline prevalence in 51% of the participants for the respective screening setting (21,24). Trials with a detection limit of 4 mm or greater (IELCAP, NLST, ITALUNG, LUSI) reported a lower non-calcified pulmonary nodule rate of between 13%~30% at baseline (6,26-28). This suggests that a great number of non-calcified pulmonary nodules at baseline are small pulmonary nodules. Of the trials with no or a low detection limit, the Mayo trial reported that 39% (307/780) of participants only had non-calcified pulmonary nodules smaller than 4 mm and the NELSON trial found that 56% (4,861/8,623) of the non-calcified pulmonary nodules detected at baseline were smaller than 50 mm^3 (roughly 4.7 mm) (24,31,33). Within the baseline round of the DLCST trial, 66% (371/560) of the non-calcified pulmonary nodules were below 5 mm and in baseline participants of the ELCAP trial, the largest non-calcified pulmonary nodule was smaller than 5 mm in 58% (136/233) (23,30,34).

Concluding, evidence from trials with no or a low detection limit indicates that 22%~51% of heavy smokers and former heavy smokers have non-calcified pulmonary nodules at baseline screening. Of the non-calcified pulmonary nodules detected at baseline, possibly up to 56% are small pulmonary nodules below 50 mm^3 or 5 mm.

Lung cancer risk of participants with non-calcified pulmonary nodules at baseline and lung cancer probability of non-calcified pulmonary baseline nodules

Unfortunately, data regarding the overall lung cancer risk of participants with baseline nodules is not frequently described. Trials rather report how many participants are

Table 2 Baseline results of selected American low-dose computed tomography lung cancer screening trials and the IELCAP trial

Variables	NLST (28,29)	ELCAP (30)	IELCAP (6)	Mayo[†] (31)	PLuSS[†] (5,32)
Participants					
Received CT screening	26,309	1,000	31,567	1,520	3,642
Age, mean (SD)[‡] or median (IQR)[§]	NA	67 (NA)[§]	62 (NA)[§]	59 (NA)[‡]	59 (NA)[‡]
Pack years, mean (SD)[‡] or median (IQR)[§]	NA	45 (NA)[§]	30 (NA)[§]	45 (NA)[§]	47 [33–62][§]
Nodule detection limit	≥4 mm	None reported[¶]	≥5 mm	None reported	None reported
Participants with lung cancer	270/26,309 (1.0%)[††]	27/1,000 (2.7%)	405/31,567 (1.3%)	31/1,520 (2.0%)	53/3,642(1.5%)
Participants with NCNs	7,041/26,309 (26.8%)	233/1,000 (23.3%)	4,186/31,567 (13.3%)	780/1,520 (51.3%)	1,477/3,642 (40.6%)
% with lung cancer	267/7,041 (3.8%)	27/233 (11.6%)	405/4,186 (9.7%)	31/780 (4.0%)	53/1,477 (3.6%)
% of NCNs being lung cancer	NA	27/363 (7.4%)	NA	31/1,646 (1.9%)	53/2,497 (2.1%)
Lung cancer					
Stage I	155/270 (57.4%)	23/27 (85.2%)	348/405 (85.9%)	22/31 (71.0%)	31/53 (58.5%)
Histology					
Adenocarcinoma[‡‡]	156/270 (57.8%)	21/27 (77.8%)	NA	23/31 (74.2%)	NA
Squamous-cell carcinoma	47/270 (17.4%)	1/27 (3.7%)	NA	4/31 (12.9%)	NA
Small-cell Lung cancer	15/270 (5.6%)	0	NA	2/31 (6.5%)	1/53 (1.9%)
Others	52/270 (19.3%)	5/27 (18.5%)	NA	2/31 (6.5%)	NA

[†], the Mayo and PLuSS trials reported their baseline findings including lung cancers found in baseline nodules during incidence screening rounds; [¶], participants with more than 6 NCNs were not reported as having lung nodules; [††], low-dose CT detected lung cancer cases; [‡‡], bronchioloalveolar carcinomas are considered adenocarcinomas. NLST, National lung screening study; ELCAP, early lung cancer action project; IELCAP, international early lung cancer action project; Mayo, Mayo CT Screening study; PLuSS, Pittsburg Lung Screening Study; SD, standard deviation; IQR, interquartile range; NCNs, non-calcified pulmonary nodules; NA, not available.

diagnosed with lung cancer per round, irrespective in which round the nodule was found initially. However, information about the overall lung cancer risk is crucial, since it could directly influence the clinical practice approach of incidentally found lung nodules in smokers and provide essential information for the development of new guidelines.

The Mayo trial (5-year results) and PluSS trial (3-year result) report that 4% (31/780 and 53/1,477 respectively) of participants with a non-calcified pulmonary nodule at baseline developed cancer in such a nodule within their screening program (31,32). Both trials did not employ a detection limit. The NELSON trial, which used a 15 mm^3 (roughly 3 mm) detection limit, reported a 2-year lung cancer risk of 3% (94/3,189) for Dutch participants with baseline nodules (35).

Regarding the probability of a non-calcified pulmonary baseline nodule being diagnosed as lung cancer eventually, the Mayo trial (5-year results) and PLuSS trial (3-year results) reported that 2% (31/1,646 and 53/2,497 respectively) of the non-calcified baseline nodules turned out to be lung cancer (31,32).

The other trials included here, only reported the baseline detection rate, thus the number of lung cancers found in participants at baseline, ranging between 1%~3% for all participants (6,21,22,24-27,30,34), and 2%~11% for participants with non-calcified pulmonary baseline nodules (6,21,24-27,29,30,34). During baseline screening, the probability of a non-calcified pulmonary baseline nodule being detected as lung cancer ranged between 1–7.4% (23,24,26,35). In particular, the ELCAP and IELCAP trial reported very high lung cancer rates [12% (27/233) and 10% (405/4,186) respectively] for participants with non-calcified pulmonary nodules during baseline screening (6,30). However, as demonstrated previously, these trials

also reported a low non-calcified pulmonary nodule overall detection rate (6,30). Apparently, the screening methodology of these studies enabled an efficient manner of recognizing individuals with high-risk pulmonary nodules, while potentially not detecting or registering unsuspicious nodules.

As mentioned before, the UKLS and NELSON trial share a similar screening methodology; however, the participant recruiting strategy differed significantly. While inclusion in the NELSON trial was mainly based on age and smoked pack-years (24,36), the UKLS trial used a multivariate conditional logistic regression model (including: smoking duration, selected prior respiratory diseases, occupational exposure to asbestos, prior diagnosis of malignant tumors and early onset family history of lung cancer) based on the Liverpool Lung Project (21,37,38). The UKLS trial included participants only if their calculated 5-year lung cancer risk was more or equal to 5% (21). This difference in selection methodology resulted in an older screening population in the UKLS if compared to the NELSON trial (mean age: 67 vs. 59 years) and an increased lung cancer baseline detection rate in participants with non-calcified pulmonary baseline nodules [4.1% (42/1,015) *vs.* 1.8% (70/3,816)] (21,24,25). This unique comparison, which is made possible due to the similar screening methodology, demonstrates the impact of pre-test probability and the limited comparability even of methodologically similar lung cancer screening trials.

Concluding, the sparse existing evidence from the Mayo, PLuSS and NELSON trial indicates that 3%~4% of heavy smokers or former heavy smokers with non-calcified pulmonary nodules at baseline screening will be diagnosed with lung cancer in such a nodule within 2–5 years (assuming similar epidemiology as in these trials). However, as demonstrated through baseline lung cancer detection rates of the other mentioned trials, depending on screening protocol and disease prevalence within the screened population, the number may be significantly higher. The translation from lung cancer screening trials to clinical management of incidentally detected nodules relies on careful assessment of the study population from which the data was generated.

Stage and histology of lung cancers found in non-calcified pulmonary baseline nodules

Only the Mayo and PLuSS trial reported data in a way enabling assessment of lung cancers found in non-calcified pulmonary baseline nodules across all screening rounds. Most lung cancers detected in a non-calcified pulmonary baseline nodule were stage I [Mayo: 71% (22/31), PLuSS: 59% (31/53)] (31,32). Only the Mayo trial provided information concerning the histology of lung cancer found in non-calcified pulmonary baseline nodules during all screening rounds. The majority [74% (23/31)] of lung cancers were adenocarcinomas, followed by squamous- cell carcinomas [13% (4/31)] and small-cell lung cancer [7% (2/31)].

The results concerning stage and histology at baseline screening are equivocal. The ELCAP trial, IELCAP trial, and LUISI trial reported a very high proportion of stage I lung cancer at baseline (82%~86%) (6,27,30). The other trials, including the two largest, randomized controlled trials (NLST and NELSON), reported lower numbers regarding stage I lung cancers (48%~67%) (7,21,22,24,26,27). There is no data available about differences in stage or histology distribution between non-calcified pulmonary baseline nodules identified as lung cancers at baseline compared to non-calcified pulmonary baseline nodules identified as lung cancers in later rounds. Differences between lung cancers found at baseline and incidence rounds, as published for instance by the ELCAP trial (39), cannot be used for the here performed assessment, since observed variances may be due to lung cancers found in newly detected nodules.

Concluding, lung cancers detected in non-calcified pulmonary baseline nodules are mostly adenocarcinomas. Current evidence suggests that only a small fraction is small-cell lung cancer. At baseline, lung cancers are stage I in 48%~86% of the cases. Data concerning stage distribution of lung cancers detected in baseline nodules at subsequent rounds is sparse.

New non-calcified pulmonary nodules in incidence screening rounds of LDCT lung cancer screening

Prevalence of new non-calcified pulmonary nodules in incidence rounds of LDCT lung cancer screening

As pointed out by several studies and the recently released British Thoracic Society guidelines for the Investigation and Management of Pulmonary Nodules, little evidence exists concerning pulmonary incident nodules that appear after baseline screening and are not visible in retrospect (10,19,40). In 2005, the Fleischner society reported, citing the Mayo trial, that 10% of screening participants develop a new nodule not present in retrospect within a

1-year interval, and the PLuSS trial described that 7% (256/3,423) of their participants developed a new nodule in the same interval (32,33,41). Numbers from the ELCAP and IELCAP publications suggest annual new nodule rates of 3% (40/1,184) and 5% (1,460/27,456) respectively in LDCT lung cancer screening (6,42). In the annual screening round of the NELSON trial, 5% (344/7,295) of participants developed a new non-calcified solid nodule, while a total of 11% (787/7,295) of participants developed a new non-calcified solid nodule within the first two incidence screening rounds (3 years after baseline) (40).

The NELSON trial reported that 57% (697/1,222) of the newly detected nodules were small pulmonary nodules with a volume less than 50 mm^3 (roughly 4.7 mm) (40). The ELCAP trial reported that in the 30 participants with high-resolution CT confirmed new non-calcified pulmonary incident nodules, the largest nodule had had a diameter less than 5 mm in 53% (16/30) of participants (42), and in 37% (70/191) of participants with new non-calcified pulmonary incident nodules in the Mayo trial, the nodules were smaller than 4 mm (33).

Concluding, current evidence suggests that 3%~10% of LDCT lung cancer screening participants may develop a new non-calcified pulmonary incident nodule annually and up to 57% of these nodules are pulmonary nodules smaller than 50 mm^3 or 5 mm.

Lung cancer risk of participants with new non-calcified pulmonary incident nodules and lung cancer probability of new non-calcified pulmonary incident nodules

The evidence regarding lung cancer probability of new non-calcified pulmonary incident nodules is scarce. Furthermore, differing methodologies of trials make the numbers hardly comparable.

The NELSON trial recently reported that 6% (49/787) of participants with a new non-calcified solid nodule developed lung cancer in such a nodule, with 4% (50/1,222) of the new non-calcified solid incident nodules proving to be lung cancer (40). The ELCAP trial reported that 10% (4/40) of participants with new non-calcified pulmonary incident nodules on LDCT had lung cancer in a new nodule, and the IELCAP reported this was the case for 5% (74/1,460) of its participants (6,32,42). The Mayo trial found a lower rate of 1.6% (3/191) (33). However, the Mayo trial reported a substantially higher new nodule rate than the other trials (see above) and the clinic where the trial was performed is located in an area with a high prevalence of histoplasmosis (20). This may explain why the Mayo trial found the highest new nodule rate, but the lowest cancer rate in new non-calcified pulmonary incident nodules. Without providing numbers, the NLST reported that detection of new non-calcified pulmonary incident nodules in the second incidence screening round was predictive for cancer if compared to stable nodules (43).

Concluding, there is only little evidence concerning the lung cancer risk of participants with new non-calcified pulmonary incident nodules. The two large studies that provide data (IELCAP and NELSON trial) show that in 5%~6% of participants with new non-calcified pulmonary incident nodules, such a nodule proves to be lung cancer. The only available numbers concerning lung cancer probability of new (solid) incident nodules come from the NELSON trial, where 4% of the new solid non-calcified pulmonary incident nodules proved to be lung cancer.

Stage and histology of lung cancers found in new non-calcified pulmonary incident nodules

The only trial to provide explicit data concerning lung cancer stage, as well as histology for new incident nodule lung cancer, is the NELSON trial. It was found that 68% (34/50) of the new incident nodule lung cancers were detected at stage I (40). Of the detected lung cancers 38% (19/50) were adenocarcinomas, 22% (11/50) were squamous-cell carcinoma, and 10% (5/50) were small-cell lung cancer. The IELCAP trial reported that 86% (64/74) of lung cancers in patients with new non-calcified pulmonary incident nodules was detected at stage I (6).

Concluding, it appears that thorough LDCT lung cancer screening can detect most new nodule lung cancer at an early and still treatable stage. There is insufficient data to make definite statements about cancer histology of new nodule lung cancer detected in incidence screening rounds of LDCT lung cancer screening.

Comparing lung cancer probability of small pulmonary nodules detected at baseline and newly detected during LDCT incidence screening

Due to the differences in screening methodology, baseline nodules and new incident nodules should not be compared across lung cancer screening trials. Valid conclusions can only be reached through analysis within one screening trial. Furthermore, because only a subgroup of participants

develops new incident nodules, trials have to be large enough to provide a significant sample size of new nodule lung cancers.

The IELCAP trial reported a cancer rate of 10% (405/4,186) in participants with baseline nodules and a cancer rate of 5% (74/1,460) for participants with new non-calcified pulmonary incident nodules (6). However, it is crucial to note that the screening method for baseline and incidence screening deviated significantly. While during the baseline screening round only nodules greater or equal to 5 mm were registered, there was no detection limit for new non-calcified pulmonary incident nodules at incidence screening rounds (6). The cancer rate at baseline excluded participants who only had nodules smaller than 5 mm, which as seen in other trials comprise the largest group of nodules, but the cancer rate for new incident nodules included them, rendering the numbers incomparable.

The ongoing NELSON trial did not yet provide the cancer rate of nodules detected at baseline for the overall screening. A comparison of cancer probability of new non-calcified pulmonary incident nodules and non-calcified pulmonary baseline nodules has to be made indirectly. In the baseline screening round of the NELSON trial, 1% (70/7,557) of participants were detected with lung cancer (24), and within the first three screening rounds, 3% (200/7,582) participants had screen-detected lung cancer (including 44 cancers detected in new solid non-calcified pulmonary incident nodules) (25,40). As mentioned before, the 2-year cancer risk of participants detected with baseline nodules in the NELSON trial has been reported to be 3% (94/3,189). The cancer risk of participants detected with new solid non-calcified pulmonary incident nodules was 6% (49/749). Comparing these numbers, new solid non-calcified pulmonary incident nodules appear to have a higher lung cancer probability than do non-calcified baseline nodules. This is underlined by the fact, that the overall cancer risk of participants with a new solid non-calcified pulmonary incident nodule was similar to the risk of participants with a suspicious nodule at baseline that required further follow-up (40).

New incident nodules are considered fast-growing and some lung cancer screening trials and screening guidelines anticipated this by using different cut-off values for baseline nodules and new incident nodules (6,44,45). The NELSON trial showed that there is a significant difference in the lung cancer probability of small pulmonary non-calcified nodules already present at baseline and new non-calcified pulmonary incident nodules. Within the NELSON trial, baseline nodules that were smaller than 100 mm^3 (roughly 5.8 mm) had a lung cancer probability of about 0.5–0.7%, which statistically did not differ from participants without baseline nodules (35). It was concluded that these nodules do not necessitate follow-up. However, this does not apply in case of new solid non-calcified pulmonary incident nodules, where 3% of participants whose largest new nodule was smaller than 100 mm^3 (roughly 5.8 mm) were eventually diagnosed with lung cancer, with 2% (15/819) of new solid non-calcified incident nodules smaller than 100 mm^3 (roughly 5.8 mm) found to be lung cancer (40). These findings caused the NELSON investigators to propose different cut-off values for the follow-up of baseline nodules and new solid non-calcified pulmonary incident nodules. Based on the results of the NELSON trial, non-calcified baseline nodules smaller than 100 mm^3 (0.6% lung cancer probability) or 5 mm (0.4% lung cancer probability) may continue in regular screening, non-calcified baseline nodules 100–300 mm^3 (2.4% lung cancer probability) or 5–10 mm (1.3% lung cancer probability) represent an indeterminate subgroup requiring follow-up with volume doubling time measurement (<600 days necessitates further follow-up), and, non-calcified baseline nodules greater than 300 mm^3 (16.9% lung cancer probability) or 10 mm (15.2% lung cancer probability) should be referred for immediate diagnostic evaluation (35). New non-calcified pulmonary incident nodules require a more aggressive follow-up strategy and only a new non-calcified solid incident nodule smaller than 27 mm^3 (0.5% lung cancer probability) or 3.7 mm (0.6% lung cancer probability) should continue regular screening, new non-calcified solid incident nodules between 27–206 mm^3 (3.1% lung cancer probability) or 3.7–8.2 mm (3.0% lung cancer probability) represent an indeterminate subgroup requiring follow-up and volume doubling time measurement, and new non-calcified pulmonary incident nodules greater or equal 206 mm^3 (16.9% lung cancer probability) or 8.2 mm (14.2% lung cancer probability) should be referred for immediate diagnostic evaluation (40). This verifies part of the LungRads guidelines as provided by the American College of Radiologists (44). It has been suggested that the findings regarding new nodules may be translated directly into routine clinical practice for the respective risk group (i.e., smokers or former heavy smokers) outside a screening program, if the nodule can be proven to be newly developed within 1–2 years (40,46).

The explanation for the different lung cancer probabilities at smaller sizes of non-calcified baseline and

new non-calcified pulmonary incident nodules could be the fact that compared to new incident nodules, baseline nodules had more time to grow before their first detection. Therefore, growing baseline nodules which possess a higher lung cancer probability are larger, while even fast growing new nodules may still be relatively small at initial detection. Furthermore, new non-calcified pulmonary incident nodules may be inherently more likely to be cancer than non-calcified baseline nodules. Nevertheless, more evidence is necessary to expand existing evidence.

Conclusions

Reporting lung cancer screening results per round, without providing overall cancer risks of participants detected with non-calcified pulmonary nodules at baseline or with new non-calcified pulmonary incident nodules at subsequent screening rounds, only provides limited information on lung cancer probabilities of the respective nodule groups. Much evidence is to gain from a more standardized manner of reporting, including subgrouping of the detected nodules according to the moment of the first detection, such as baseline nodule or new incident nodule. This would also simplify the translation to the current clinical practice of incidentally detected nodules.

Around half of heavy smokers or former heavy smokers may present with non-calcified pulmonary nodules at baseline screening. Though there only is limited evidence, it can be expected that at least 3%~4% of these individuals will be diagnosed with lung cancer in a non-calcified pulmonary baseline nodule within the next 2–5 years. The majority of non-calcified pulmonary nodules detected at baseline are pulmonary nodules smaller than 50 mm^3 or 5 mm and possess a low lung cancer probability.

Furthermore, 3%~10% of heavy smokers or former heavy smokers develop a new non-calcified pulmonary incident nodule annually, and these nodules prove to be lung cancer in 5%~6% of participants. Internal comparison of the NELSON trial provided evidence that new non-calcified pulmonary incident nodules possess a greater lung cancer probability than baseline nodules at a smaller size. This may be due to the reduced time they had to grow before first nodule detection, or due to an inherently increased cancer probability. Therefore, small pulmonary non-calcified nodules detected newly at lung cancer incidence screening rounds should be followed up more aggressively than small pulmonary non-calcified nodules detected at baseline screening. Additionally, for the respective risk population, the findings may be extrapolated for the management of incidentally detected nodules in routine clinical care, outside a screening program.

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Footnote

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Volume versus diameter assessment of small pulmonary nodules in CT lung cancer screening

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Abstract: Currently, lung cancer screening by low-dose chest CT is implemented in the United States for high-risk persons. A disadvantage of lung cancer screening is the large number of small-to-intermediate sized lung nodules, detected in around 50% of all participants, the large majority being benign. Accurate estimation of nodule size and growth is essential in the classification of lung nodules. Currently, manual diameter measurements are the standard for lung cancer screening programs and routine clinical care. However, European screening studies using semi-automated volume measurements have shown higher accuracy and reproducibility compared to diameter measurements. In addition to this, with the optimization of CT scan techniques and reconstruction parameters, as well as advances in segmentation software, the accuracy of nodule volume measurement can be improved even further. The positive results of previous studies on volume and diameter measurements of lung nodules suggest that manual measurements of nodule diameter may be replaced by semi-automated volume measurements in the (near) future.

Keywords: Semi-automated volume measurement; manual diameter measurement; small pulmonary nodule

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Introduction

Lung cancer is the leading cause of cancer-related mortality in men and women worldwide (1). This is mainly due to the fact that lung cancer patients are mostly asymptomatic in early stages. Patients presenting with symptoms such as cough or chest pain in the clinics often already have advanced lung cancer with very limited survival time despite of treatment. Therefore, early detection of lung cancer is extremely important.

The National Lung Screening Trial (NLST), a large-scale randomized controlled trial including over 53,000 participants, has demonstrated that low-dose computed tomography (LDCT) screening for individuals at high risk for lung cancer, reduced lung cancer mortality by 15%~20%, when compared to chest radiographs (2). The result of NLST was translated by several U.S. medical associations, including the U.S. Preventive Service Task Force, into recommendation for lung cancer screening using LDCT for high-risk individuals (3,4). Since February 2015, lung cancer screening for high risk individuals is covered by Medicare (5).

Despite of the benefits regarding lung cancer related mortality reduction brought by LDCT lung cancer screening, a major drawback of lung cancer screening is its high rate of false-positive screen results. A challenging problem in lung cancer screening is the high prevalence of small-to-intermediate sized (<500 mm^3 or <10 mm) lung nodules found in LDCT lung cancer screening. Up to 66% of participants enrolled for LDCT lung cancer screening have at least one lung nodule, with the large majority being benign (6). Across all three screening rounds of the NLST, 24.2% of participants received a positive screen

result, 96.4% of these were false-positive (2). Although most nodules were classified as benign by non-invasive follow up scans, false-positive screening results may cause anxiety and unnecessary invasive diagnostic procedures in some participants, which may come with complications and increased healthcare cost. In order to reduce the false-positive rate, a method to accurately identify malignant nodules is required.

Diameter measurements are widely used in CT lung cancer screening. Due to its simplicity, it is easily applicable and it is currently the main method worldwide for measuring lung nodule size. A number of medical associations have incorporated diameter measurement in their recommended nodule management protocol, including the Fleischner society lung nodule recommendations and the Lung CT screening reporting and data system (Lung-RADS) (7,8). With the advent of thin slice CT, more than a decade ago, as well as the availability of three-dimensional segmentation software, semi-automated volume measurements of lung nodules have become a valuable alternative option. The Dutch-Belgian lung cancer screening trial (NELSON) is the first large scale lung cancer screening trial that based its nodule management protocol on semi-automatically measured volume of lung nodules instead of manually measured diameter, and on nodule growth in terms of volume-doubling time. Implementation of an extra screen result for indeterminate lung nodules (volume 50–500 mm^3 or volume-doubling time (VDT) 400–600 days at incidence screens) leading to an extra short term LDCT, had led to a far lower false-positive rate compared to NLST (1.7% *vs.* 26.6%), a comparable sensitivity (92.5% *vs.* 93.5%) and a significantly higher specificity (98.3% *vs.* 73.4%) at baseline (2,9).

Several nodule characteristics were shown to be associated with lung cancer. Lung nodule margin may also help with differentiation of malignant from benign nodules. Spiculated and lobulated nodules have higher probability of being malignant compared to round nodules with smooth margin (10-13). However, nodule size and nodule growth rate were found to be most important predictors (14-19).

In lung cancer screening management protocols, nodules are divided to different risk groups by diameter or volume-based cutoffs for new nodules, and nodule growth or growth rate cutoffs for existing ones. Accurate nodule size estimation is necessary for correct classification of nodules to their risk groups. Misclassification of a nodule could potentially result in under- or overestimation of its malignancy probability, misdiagnosis or over-diagnosis of lung cancer, along with increased frequency of unnecessary invasive diagnostic procedures.

This review first focuses on the two largest CT lung cancer screening studies that have used diameter or volume measurements for the estimation of lung nodule size. Secondly, inter- and intrareader variability studies for both volume and diameter measurement will be discussed. Thirdly, an overview of recent phantom studies focusing on the accuracy and precision for volume- and diameter based measurement will be provided. Fourthly, the influence of CT-scan and reconstruction parameters on volume measurements will be discussed. Finally, future perspectives on lung nodule measurements will be proposed.

Lung cancer screening

In the NLST, nodule management was based on manually-measured maximum nodule diameter, or diameter growth on follow-up CTs. Participants with nodules of ≥4 mm or with increase in diameter of at least 10% were considered screen positive (20). However, for a nodule 4 mm in diameter, a 10% increase would mean 0.4 mm, which lies within the range of the 95% confidence interval of manual measurements of small nodules.

To reduce the high false positive rate of the NLST, the American College of Radiology released Lung CT Screening Reporting and Data System (Lung-RADS), a classification system for LDCT lung cancer screening. According to Lung-RADS, lung nodules are classified based on maximum diameter for round nodules and based on mean diameter measurement (mean of maximum transverse diameter and perpendicular diameter) for non-round nodules, instead of the use of only maximum diameter in NLST. The diameter cut-off for benign nodules has been increased from 4 to 6 mm. Two intermediate categories, which are also considered as positive result were added, a 6–8 mm category (6-month follow-up) and an 8–15 mm category (3-month follow-up). Growth has been defined as a 1.5 mm increase in diameter, instead of the 10% criterion in the NLST protocol. A growing nodule will be moved up from its original category to a higher risk category, requiring more intensive management. Additionally, nodules presenting with additional imaging findings such as spiculation, ground glass nodule that doubles in size within a year, as well as enlarged lymph nodes may be classified into a higher risk group.

The increase of cut-off for benign nodules may decrease the sensitivity for malignant nodules. In a retrospective

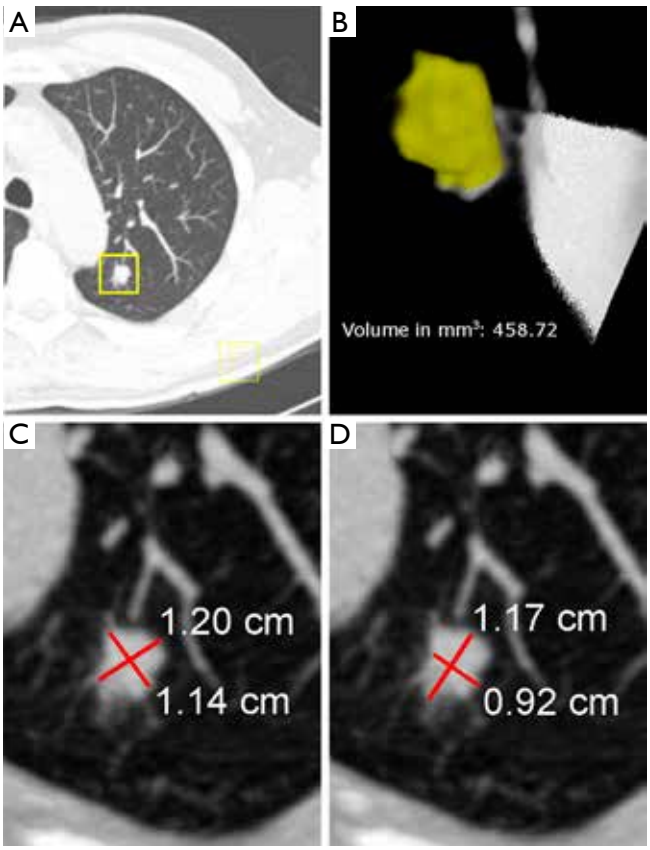

Figure 1 Transverse images of a solid pulmonary nodule and its location (A), semi-automatically assessed volume (B) and two possible manual diameter measurements (C) and (D).

study, where Pinsky *et al.* applied Lung-RADS criteria to the NLST protocol, it was found that Lung-RADS protocol showed a higher specificity when compared to the NLST protocol (87.2% *vs.* 73.4%). However, the lung cancer sensitivity of Lung-RADS is lower than NLST (84.9% *vs.* 93.5%) (3). In another study, where Lung-RADS was applied to a total of 2,180 screening subjects with high-risk for lung cancer, of which 577 (26%) of patient's clinical follow-up was unavailable, McKee *et al.* have shown that reclassifying nodules between 4 mm and 6 mm in diameter from a positive to a negative screen result did not cause an increase in false-negative results (4). However, in this study the number of nodules that were reclassified, only 152, was limited. Given in NLST, nodules of this size category (4–6 mm) had a positive predictive value for lung cancer of 0.5% (2), and 0.8 out of the 152 nodules predicted to be false positive. Therefore, more research is needed to confirm these results.

The NELSON trial is a large-scale randomized-controlled lung cancer screening trial investigating whether LDCT can reduce lung cancer related mortality by 25% compared to no screening at 10-year follow-up. One of the main differences between NELSON and NLST is the fact that whereas NLST used nodule diameter as its indicator to assess nodule size and growth, NELSON used semi-automatically measured nodule volume. In contrast to NLST, which followed a black and white approach in classifying nodules, NELSON introduced an intermediate screen result (volume 50–500 mm^3) for nodules with highest uncertainty in their nature, in addition to a negative screen result (volume <50 mm^3) and a positive screen result (volume >500 mm^3). Screenees with an indeterminate result received a short-term follow-up by low-dose chest CT. Nodules that had grown by 25% in volume at the short term follow-up CT, and had a VDT <400 days, were considered to be positive. Although the final results of the NELSON trial are still awaited, it was found that the NELSON strategy led to a much higher positive predicted value compared to diameter-based protocols, with comparable lung cancer sensitivity and negative predictive value (9).

Inter- and intrareader variability of nodule volume and diameter

Inter- and intrareader variability studies have played an important role in the development of reliable diagnostic tools, and understanding of the variability of screening outcomes in the field of lung cancer screening. A measurement method that yields low inter- and intravariability results in consistent treatment recommendations. For this, a measurement needs to be objective and has to be an accurate representation of the true size of the object that is being measured. It is therefore logical to assume that estimating nodule size by semi-automated volume measurements is a superior method compared to manual diameter measurements (*Figure 1*). Since there is limited number of studies that compare inter-and intrareader variability of small-sized lung nodule measurements, studies comparing volume- and diameter measurements of larger lesions will also be discussed.

In a study where 54 solid nodules were measured diameter wise by multiple radiologists, Revel *et al.* found that for intrareader variability, 1.6 mm growth cut-off would ensure the detection of true growth, while for multiple radiologists a 1.7 mm growth cut-off would ensure the detection of true growth (21). This study was performed with a single CT scan. It is known that lung nodules are

rarely symmetrical or spherical in shape, and the variation of inspiration level during CT scanning can cause nodules to be scanned at a differing rotational position, thus adding additional variability to diameter measurements. "Coffee break" studies, where measurement variability is evaluated after repeat CT scans within 15 minutes, can demonstrate the inherent variability of inspirational variation. In a study where 30 non-small cell lung cancers with mean lesion size of 3.7 cm (range, 1.0–8.0 cm) were evaluated for measurement variability using repeat CT scans within 15 minutes, the 95% limits of agreement was found to be ±4.8 mm, and 33% of nodules had measurement differences between radiologists greater than 2 mm (22). Yet, several other factors may have contributed to the large variability found in this study. Firstly, tumors in this study were much larger in size compared to the study by Revel *et al.* Although not statistically significant (P=0.06), Oxnard *et al.* have found that larger lesions tended to have larger measurement variability, when compared to smaller nodules. Secondly, the morphology of these 30 tumors had not been described, as non-smooth lesions may yield larger measurement variation compared to smooth nodules. Nevertheless, the result of these studies questions the reproducibility of manual diameter measurements of lung nodules.

Zhao *et al.* evaluated the inter- and intra-scan variability of 32 lesions [mean size: 37.2 mm (range, 10.7–81.5 mm)] of three radiologists (23). The radiologists were blinded and the order of the scans were randomized. For the evaluation of measurement repeatability, the first and the second radiologist had 2 days between two repeat reading sessions, while for the third radiologist all readings were done in one session. The 95% limits of agreement for unidimensional intra-scan and inter-scan variability varied greatly among the three radiologists and were ±10.2% and ±16.9% for the first radiologist, ±19.2% and ±21.8% for the second radiologist, and ±25.9% and ±22.9% for the third radiologist. Interestingly, the third radiologist who did all the readings in one session, did not show better repeatability compared to other radiologist. Although all of the 95% limits of agreement from this study fell within the guideline of Response Evaluation Criteria in Solid Tumors (RECIST) where 30% diameter increase is considered as significant growth, this study showed that measurement variability of manual diameter measurements varies greatly between readers.

The variability of diameter measurements is influenced by repeat scans. Due to the difference in inspirational level, the maximum transverse diameter of an asymmetrical lung nodule can vary greatly between two consecutive scans because of the difference in nodule rotation. Therefore, it is reasonable to assume the volume of the nodule to stay constant, while maximum diameter might be different on repeat scans. In a study where Gietema *et al.* evaluated interobserver variability of semi-automated volume measurements (24), 47/430 (11%) nodules had interobserver variability while the rest of the lung nodules 383/430 (89%) did not. The 95% limits of agreement of these 47 nodules in which interobserver variability occurred, was found to be ±25.2%. In another study, Gietema *et al.* evaluated the influence of lung nodule size, inspiration level, and nodule morphology on volume measurement variability of repeat scan within 15 minutes while using the same volume measurement software (25). The 95% limits of agreement for a total of 218 nodules was ±22.5%, which is comparable to ±25.2% found for nodules that had interobserver variability in the previous study. For nodules that were completely segmented by measurement software, the inspiration level was only weakly related to the measurement precision. The influence of nodule shape on the measurement precision was found to be significant (P<0.001), considering spherical nodules and nonspherical nodules had 95% limits of agreement of ±12% and ±28.4%, respectively. It was suggested to set the growth cut-off for semi-automated volume measurements of spherical nodules at 15% whereas for nonspherical nodules to be set at 30%. However, nonspherical nodules can also be subdivided to lobulated, spiculated, and irregular based on nodule margin, each may influence on measurement variability by different extent. By adopting separate growth cut-off for each nodule morphological categories more optimal nodule management in lung cancer screening might be achieved.

Several other "coffee break" studies have found similar limits of agreement for automated nodule volume measurements. In the study by Wormanns *et al.* the 95% limit of agreement was ±21.3% (26), while Goodman *et al.* reported a 95% limit of agreement of ±25.6% (27). Hein *et al.* compared the interscan interreader variability between standard-dose CT and ultra-low dose CT, and reported maximum 95% limits of agreement of ±27% (28). The similarity of this value compared to values reported in the literature for low-dose CT scanners suggests that semi-automated volume measurement at ultra-low dose is feasible without compromising the precision of volume measurement.

One important point is that volume measurement works conjointly with its semi-automatic function. The benefit of volume measurement alone cannot be clearly seen through

the comparison between manual diameter measurement and semi-automated measurement, as it is not known how much does the automatic function plays part. By comparing semi-automated diameter measurement with semi-automated volume measurement, the true benefit of volume measurement can be shown. Zhao *et al.* have compared the semi-automated diameter measurement with semi-automated volume measurement of lung tumors, where he concluded that growth cut-off, based on the 95% limit of agreement, for semi-automated diameter measurement should be set at 8%, while for semi-automated volume measurement it should be set at 15%. Since the mean tumor size in this study varied from 34 to 37 mm in diameter depending on the reader, for a hypothetical spherical tumor of 35 mm in diameter assuming the tumor to be a perfect sphere, a variation of 8% in diameter, would result in measurement variability of around 25% in volume compared to the 15% cutoff for volume measurements as set by the authors. The low measurement variability compared to other studies found in literature may be pointing to the relation between nodule/tumor size and measurement variability. A disadvantage of comparison between two types of semi-automated measurements is that the performance can vary between measurement softwares. Since it is unknown how the two software programs in the above mentioned studies perform compared to other commercially available softwares, one needs to be cautious when making conclusion of which type of measurement has better accuracy and precision.

Studies discussed so far focused on measurement of static lung lesions. Studies of lung lesions that are tested to be sensitive to targeted therapy can help to demonstrate the sensitivity and specificity of volume and diameter measurement at detecting size change of lesions. Zhao *et al.* compared the sensitivity of diameter and volume measurements in detecting size shrinkage of lung lesions as a response to gefitinib treatment, for lung tumors with and without EGFR sensitizing mutations (29). The optimal threshold for detecting response to gefitinib treatment were determined to be 7.0% and 24.9% in decrease in diameter and volume, respectively. For diameter measurements, the sensitivity for detecting the response of EGFR sensitizing mutations was 71% while specificity was 78%, whereas for volume measurements, the sensitivity was 90% and specificity 89%. Although the study focused on the measurement of lung masses instead of lung nodules, the superiority in sensitivity and specificity of volume measurement in detecting change in size of tumors suggests similar performance difference also applies for smaller lung nodules.

In summary, although limit of agreement for both manual diameter measurements and semi-automated volume measurements for the studies discussed above lies in the same range in terms of absolute percentages, the percentage of lung nodules in which an actual inter-reader difference found was with 11% far lower for semi-automated nodule volume measurements compared to manual diameter measurements, where inter-reader variability occurs commonly. Furthermore, the extra dimension in volume measurements should be taken into account. Assuming a nodule as a sphere, a variation of 20% in nodule diameter, which is commonly found in the different studies, refers to a variation of 72% in nodule volume.

Phantom studies

Up until now, static and dynamic lung nodules and tumors have been discussed. However, a disadvantage of patient studies is that the true size of lung nodules is not known. CT phantom studies, although less representative of CT scans in the clinical setting, allows CT-derived nodule size assessment of artificial nodules to be compared with their true size. In addition, phantom studies allow optimization of CT scan and reconstruction parameters without harming test subjects with radiation exposure.

Semi-automated volume measurements were compared to manual diameter measurements in an anthropomorphic phantom study by Xie *et al.* (30). It was reported that low-dose CT yielded more accurate volume measurement when using a semi-automated method than using a manual method. In their anthropomorphic study of measuring 15 spherical nodules of 3, 5, 8, 10, and 12 mm in diameter (corresponding to 14, 65, 268, 523 and 904 mm^3), both semi-automated volume measurement and volume derived from manual diameter measurement significantly underestimated the size of nodules of three different densities (–800, –630, +100 HU). For solid nodules (+100 HU), semi-automated volume measurements had significantly smaller underestimation when compared to manual diameter derived volume (7.6±8.5% *vs.* 26.4±15.5%). Furthermore, manual diameter measurements had significantly larger underestimation compared to semi-automated diameter measurements (9.2±6.0% *vs.* 3.7±7.1%). In addition to this, solid nodules that were smaller had larger relative underestimation in CT-derived volume measurements and diameter measurements,

when compared to larger nodules. However, there are contradicting findings from previous studies, as some have reported a similar trend of underestimation with decreasing nodule size (31,32), while others reported increasing overestimation with decreasing volume size (33-38). The so-called partial volume effect has been considered as an important contributor to potential error in semi-automated volume measurements of lung nodules. Most softwares use voxel counting method to calculate nodule volume. A problem arises when voxels consist of partly nodule tissue and partly lower density lung parenchyma. As a result, voxels around the margin of nodules would present as the average density of nodule tissue and parenchyma in relative radiodensity, seen as blurry margin. Depending on the threshold set by the measurement software, these partial-volume voxels can either be counted as part of nodule volume or can be excluded, hence resulting either over- or underestimation of nodule volume.

In a subsequent phantom study, Xie *et al.* evaluated semi-automated volume measurements of small irregular lung nodules (spiculated and lobulated ones) ranging from 5.1±0.2 to 88.4±3.4 mm^3 in volume and −51±11 to +157±8 HU in actual density (39). The CT-derived semi-automated volume of irregular nodules was significantly smaller than the actual volumes with a mean underestimation of 18.9±11.8 mm^3 (percentage underestimation: 39%±21%). The percentage underestimation for irregular nodules was found to be larger than for spherical nodules evaluated in the previous study (39±21% *vs.* 7.6±8.5%). Additionally, actual nodule volume and nodule shape were found to significantly influence CT-derived volume. However, it was found that the observer did not influence the CT-derived volume. The fact that nodules that are smaller and with complicated margin have larger measurement error compared to larger and spherical nodules, can be explained by the surface area to volume ratio (SA/V), since nodules with large SA/V ratio are more under influence of partial volume effect than nodules with low SA/V ratio such as large spherical nodules.

In summary, in phantom studies it was found that semi-automated volume measurements led to a more accurate estimation of nodule size as manual diameter measurements. However, both measurement techniques led to an underestimation of actual nodule size.

Effect of scan and reconstruction parameters

Optimization of scan and reconstruction parameters can improve the accuracy of lung nodule measurements. Several parameters have been examined on their influence on volume measurement accuracy and precision, including slice thickness and reconstruction kernel.

As explained earlier, partial volume effect can cause volume measurement errors especially in nodules small in size and with complex margins, as they have large SA/V. However, by reducing the slice thickness of CT, the voxel size can be decreased. Therefore, the influence of the partial volume effect can be reduced and measurement accuracy can be improved. The influence of slice thickness on volume measurement has been evaluated in a number of studies. Winer-Muram *et al.* have found a difference of 20% in volume measurement of tumors between thin (2–3 mm) and thick (8-10) slice thickness settings (38). Similar findings have also been reported by Petrou *et al.* (40) and Kuhnigk *et al.* (41).

In phantom studies, the influence of slice thickness on semi-automated volume measurement has been evaluated as well. In a recent study, Li *et al.* evaluated 40,000 volume measurements of 48 nodules ranging from 5 to 20 mm in size to determine factors that contribute substantially to measurement errors of lung nodule size (42). Slice thickness × collimation along with nodule size and attachment to vessels and chest wall were found to be the main factors of measurement error. Similar findings regarding slice thickness also have been reported by Winer-Muram *et al.* in which volume overestimation varied directly with section thickness (38).

In CT-imaging a compromise exists between image detail and image noise. During image reconstruction, mathematical filters, also known as reconstruction kernels, are applied to change some of the image characteristics. Detailed kernels, also known as hard kernels, are selected to enhance detail, usually at the expense of increased imaging noise, while soft kernels are selected to reduce noise in an image. However, reduction of noise usually increases blurring and reduces visibility of detail. Like the blurring caused by partial volume effect, which has an influence on nodule volume measurements, soft kernels can also influence nodule volume measurements in a similar way, by introducing blurring along the nodule margin. Ko *et al.* reported that the choice of hard or soft kernels had a significant effect on the measurement error of synthetic nodules (43). Similarly, Li *et al.* reported hard kernels yielded better repeatability coefficient than those images reconstructed using medium kernels (42).

Although hard kernels have generally yielded better

measurement results, with reduced measurement error and better precision than soft kernels, image noise remains to be a problem and can possibly affect lung nodule detectability and volume measurement. Punwani *et al.* reported decreasing sensitivity of nodule detection (>4 mm) at signal-to-noise ratio (SNR) of 1.5 and lower (44), with similar finding also reported by Li *et al.* (45). Nevertheless, Christe *et al.* reported no significant impact of noise on volume measurement (46). However, Xie *et al.* reported underestimation of nodule measurements at lower doses (30). The latter was confirmed by Willemink et al, reporting an underestimation of up to 23.9% for nodules >5 mm (47). The difference in reported results could be caused by the choice of different slice thicknesses and type of reconstruction kernel.

Future perspectives

There is an accumulating evidence that shows volume measurements of lung nodules is more accurate and reproducible when compared to diameter measurements. Through the optimization of scanning and reconstruction parameters, the accuracy and reproducibility of measurement can be further improved, reaching even closer to the physical volume of lung nodules. However, this may be lesser the case for diameter measurement.

Recently, iterative reconstruction has been introduced to CT imaging. Compared to reconstruction kernels, iterative reconstruction aims to reduce the noise of images while minimising the compromise to image detail. This allows the possibility of ultra-low dose CT-scanning (1/10 of radiation dose compared to a regular CT scan), producing CT images of image quality and detail comparable to LDCT. Sui *et al.* reported that ultra-low dose CT with iterative reconstruction had higher sensitivity in detecting lung nodules (92.1% and 92.9% for reader 1 and 2, respectively) compared to LDCT with filtered back projection (88.9% and 86.6% for radiologist 1 and 2, respectively). Furthermore, when iterative reconstruction is compared to LDCT with filtered back projection, no significant differences in nodule volume or diameter measurements were found (48).

Commercially available software can vary greatly in measurement accuracy and precision, not to mention the poor performance in measuring the size of sub-solid/part-solid nodules, due to their lower contrast ratio to the lung parenchyma. Zhao *et al.* reported significant differences in volumetric measurements from the comparison of three commercially available volume measurement softwares which could affect the classification of nodules based on their size (49). In addition to this, one of the main factors for large variability in semi-automatic volume measurement of lung nodules is vessel and pleura attachment. Therefore, the improvement of segmentation software as well as standardization of CT imaging parameters is an important part in the implementation of semi-automated volume measurement into clinical practice.

The final screen results of the NELSON trial are awaited before the decision on implementation of lung cancer screening in Europe can be made. However, with the implementation of lung cancer screening in the United States, and the high number of incidentally detected nodules in clinical care worldwide, it is of major importance to use a precise and accurate manner to estimate nodule size and detect nodule growth. The positive results of previous studies suggest that manual measurements of nodule diameter may be replaced by semi-automated volume measurements in the (near) future.

Summary

We have reviewed the comparison of semi-automated volume measurement and diameter measurement of lung nodules. Although manual diameter measurements are currently the standard in U.S. lung cancer screening programs and are used for lung nodules detected in routine clinical care, results of European screening studies using semi-automated volume measurements in terms of false-positive screen results and positive predictive value may not be neglected. There is an accumulating evidence that semi-automatic volume measurements have higher accuracy and reproducibility compared to diameter measurements. Furthermore, with optimization of CT scanners and reconstruction parameters, and advancement in semi-automated volume measurement software, the accuracy and reproducibility of volume measurements can be improved even further. The positive results of previous studies on volume and diameter measurements of lung nodules suggest that manual measurements of nodule diameter may be replaced by semi-automated volume measurements in the (near) future.

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Footnote

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Lung cancer screening guidelines: common ground and differences

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Abstract: Lung cancer accounts for almost one-third of all cancer related deaths. Lung cancer risk persists even after smoking cessation and so many lung cancers now are diagnosed in former smokers. Five-year survival of lung cancer has marginally improved over decades and significantly lags behind that of colon, breast and prostate cancer. Over the past one decade, lung cancer screening trials have shown promising results. Results from National Lung Cancer Screening Trial (NLST), have shown a significant 20% reduction in mortality with annual low dose computed tomography (LDCT) screening. Based on these results, annual LDCT testing has been recommended for lung cancer screening in high risk population. However, development and acceptance of lung cancer screening as a public health policy is still in the nascent stages. Major concerns relate to risk of radiation, overdiagnosis bias, proportion of false positives and cost benefit analysis. This article reviews the literature pertaining to lung cancer screening guidelines and above mentioned concerns.

Keywords: Lung cancer; cancer screening; low-dose computed tomography (LDCT)

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Introduction

Lung cancer is the leading cause of cancer related mortality. There are approximately 159,260 lung cancer related deaths projected for 2014 in the USA, which accounts for one third of all cancer deaths (1). Despite significant advances in medical therapy, the overall 5-year survival rate for lung cancer has only increased from 11.4% in 1975 to 16.6% in 2009 as more than half of the cases are diagnosed at a metastatic stage with a 5-year survival of 3.9% (2). Only 15% cases are stage I at the time of diagnosis, which carries a higher 5-year survival rate of 53.5% (1). These rates give a rationale for lung cancer screening in high risk populations. For decades, tobacco control strategy has remained the cornerstone of lung cancer prevention strategies (3). Despite the reduction in the prevalence of smoking among adults from 43% to 18% (4) in 2010, since the release of US Surgeon General's statement on impact of tobacco in 1964, the incidence of lung cancer has not been reduced proportionally. Smoking cessation does lowers tobacco attributable cancer risk but the risk never matches that of a non-smoker and a significant percentage of newly diagnosed lung cancers occur in former smokers (5). This pattern points to the evolving carcinogenic damage caused by tobacco smoke which continues despite cessation. Hence, combined efforts at smoking cessation and early screening seem prudent to tackle this ever increasing burden of disease. A decade has passed since the first randomized controlled trial (RCT) using low dose computed tomography (LDCT) was conducted by Garg *et al.* to assess the feasibility of early screening (6). After years of disappointing results from subsequent trials, a promising screening approach finally emerged with the National Lung Cancer Screening Trial (NLST), which is the most expensive trial ever conducted by National Cancer Institute (NCI) and spanned over a period of 9 years from 2002 to 2011. The trial reported a mortality reduction of 20% with LDCT screening as compared to chest X-ray (CXR) screening (7).

Table 1 Lung cancer screening guidelines

Society	ATS (12)	USPSTF (10)	NCCN (11)	ACS (14)	ASCO (13)
Cohort	Age 55-79 years with ≥30 pack year history of smoking; Lung cancer survivor; age ≥50 with ≥20 pack year history of smoking and added risk >5% of developing lung cancer within 5 years	Age 55-79 years with ≥30 pack year history of smoking or Smoking cessation <15 years	Age 55-74 years with ≥30 pack year smoking history and currently smoke or smoking cessation <15 years (category 1)*; OR; age ≥50 years and ≥20 pack year smoking history and one additional risk factor (other than second-hand smoke exposure) (category 2B)*†	Age 55-74 years with ≥30 pack-year smoking history, currently smoke, or have quit within the past 15 years, and who are in relatively good health	Age 55-74 years with ≥30 pack-year smoking or who have quit within the past 15 years
Screening technique and interval	Annual Low dose CT	Annual Low dose CT	Annual Low dose CT	Annual Low dose CT	Annual Low dose CT
Nodule size cut off for further imaging/surgery	>4 mm in solid nodule; ≥5 mm in Ground Glass Opacity	NA (as per NSLT)	>6 mm solid or part solid nodule	NA (as per NLST)	NA (as per NLST)

*, category 1, based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate; category 2B, based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate; †, risk factors include radon exposure, occupational exposure (e.g., silica, cadmium, asbestos, arsenic, beryllium, chromium, diesel fumes, nickel, coal smoke, and soot), cancer history, disease history (COPD, pulmonary fibrosis), and family history of lung cancer. ATS, American Thoracic Society; USPSTF, U.S. Preventive Services Task Force; NCCN, National Comprehensive Cancer Network; ACS, American Cancer Society; ASCO, American Society of Clinical Oncology; NA, not defined.

NLST is the only completed, adequately powered study for lung cancer screening in a well-defined high risk population with concrete results so far. Since the results of NLST trial, data from NELSON (8) and I-ELCAP (9) projects have also come forth with results which further support the rationale behind lung cancer screening. These results formed the basis of the screening recommendations across almost all the major societies. After an comprehensive review of the literature and existing evidence, the U.S. Preventive Services Task Force (USPSTF) (10) along with the National Comprehensive Cancer Network® (NCCN®) (11), American Thoracic Society (ATS) (12), American Society of Clinical Oncology (ASCO) (13) and American Cancer Society (ACS) (14) have appraised the use of LDCT in early diagnosis of lung cancer and have endorsed a set of guidelines for its effective implementation. European Society for Medical Oncology (ESMO), however, recommends against lung cancer screening being offered to individual patients as a routine test. Patients requesting the screening test should be referred to a comprehensive programme with assured quality control, expertise in LDCT screening and infrastructure to ensure adequate follow up. The target patient population is same as the inclusion criteria for NLST trial (15).

Guidelines for screening of lung cancer: common ground and differences

After results of the NLST (7), I-ELCAP trial (9) and preliminary data from the NELSON trial (8), various societies released guidelines for lung cancer screening. *Table 1* lists major society guidelines and pertinent follow up information wherever available. The target cohort in most of these guidelines mirrors the inclusion criteria of NSLT, which included adults between 55-74 years of age with at least 30 pack year history of smoking who were either current smokers or had quit smoking within the past 15 years. Only USPSTF has extended the upper limit of age eligible for screening till 80 years from 75 years (10). However, the consensus statement on withholding screening in individuals who quit smoking more than 15 years ago excludes a significant proportion of at-risk population, many of whom are healthy enough to undergo surgery for stage

I lung cancer. Peto *et al*. have demonstrated that the risk of lung cancer decreases with smoking cessation at an earlier age, but it never returns to baseline. The cumulative risk of lung cancer by age 75 was 10%, 6%, 3% and 2% for men who quit smoking at ages 60, 50, 40, and 30 respectively (3).

The mean age at diagnosis of lung cancer is 70 years as compared to 66 years for prostate cancer and 61 years for breast cancer (1). Consideration to include population with more than 30 pack year history of smoking under the age of 55 or individuals with a strong family history of cancer would help bridge this gap. It will also increase the rate of diagnosis at early stages of lung cancer. ATS has extended the benefits of screening to include lung cancer survivors, patients ≥50 years of age with ≥20 pack year history of smoking and an added risk of >5% to develop lung cancer within the next 5 years (12). NCCN® has a meticulous stratification of groups on the basis of age, smoking history and other risk factors (11). NCCN recommends screening in patients who meet the screening criteria of the NLST; this is a category 1 recommendation (based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate). NCCN also recommends (category 2B) screening in patients who are 50 years or older with a 20 or more pack year smoking history and at least one other risk factor (other than second hand smoke) such as radon exposure, occupational exposure, cancer history, family history of lung cancer, or history of lung disease (COPD or pulmonary fibrosis). A category 2B recommendation is based upon lower level evidence and there is NCCN consensus that the intervention is appropriate. Lower risk categories are acknowledged by NCCN but LDCT screening is not recommended due to narrower cost-benefit ratio and lack of compelling evidence.

Further research to develop more effective risk stratification tools to better define individuals at very high risk for inclusion into screening as well as to define lower risk groups which may not need the same frequency of screening is an important goal. Nevertheless, the use of current tools such as using self-reported tobacco use is an adequate tool to begin the national implementation of lung cancer screening for the United States.

Although the consensus on defining the appropriate target population for LDCT screening is very similar across the societies and for example all guidelines include provisions for informed decision making and inclusion of tobacco cessation services there is considerably more variation in regards to recommendations for follow up of a positive test result. ATS recommends follow up with 3-6 monthly imaging for a solid nodule between 4-8 mm size and ground glass opacity of more than 5 mm; and consideration for surgical removal of solid nodules more than 8 mm or nodules with rapid growth. NCCN recommends a threshold of 6 mm or more for solid and part solid nodules, and a threshold of 5 mm or more for ground glass opacities; further management depends on the size and type of the nodules and the growth pattern (11). Positron emission tomography (PET) scan can be considered for solid or part solid nodules greater than 8 mm (11). On the other hand, USPSTF, ASCO and ACS guidelines are not as detailed regarding work up of a positive result (10,13,14).

Most of these guidelines center around NLST trial results and the exploration of data from I-ELCAP and NELSON trials have been very conservatively applied. In part, related to the variability in management approach, there is still a considerable debate regarding the risks of screening. Key point is to use diagnostic work up requiring evidence of rapid nodule growth as this finding is indicative of clinically aggressive lung cancer. In this way we reduce false positive and reduce the possibility of overdiagnosis.

Overdiagnosis with LDCT annual screening

Overdiagnosis bias refers to detection of a cancer which, otherwise would never have become clinically apparent in a screening subjects' lifetime or does not behave in a lethal fashion (16). It has always been an important concern while considering the benefit of screening. The distinction between false positive rate and overdiagnosis should be acknowledged while interpreting the data. Observational studies preceding NLST trial have estimated the extent of overdiagnosis between 13% and 27% with LDCT screening (17,18). This rate was calculated to be somewhere around 18% after 6.5 years of follow up in NSLT trial (19). However, this estimate is likely to be premature and it is more than likely that with a longer follow up period, the reported incidence of overdiagnosis will decrease owing to longer natural history of some LDCT detected cancers. For example there was an initial concern of overdiagnosis with CXR screening in the prostate, lung, colorectal and ovarian cancer screening trial (PLCO trial). A recent report of the PLCO trial found that the cumulative incidence of lung cancer after long term follow-up was similar in both the CXR and the control arm in high risk population (relative risk, 1.00; 95% confidence interval, 0.88 to 1.13) (20). This new finding reduces the concern for overdiagnosis to be a major confounder in evaluating the benefit of lung

Table 2 Summary results of NLST (7) and NELSON (8) trials relative to cancer detection and stage I frequencies

Study	Round 1	Round 2	Round 1	Round 2
	No. of CAs/total screened	No. of CAs/total screened	Stage I/all detected CAs	Stage I/all detected CAs
NLST N [%]	168/24,715 [0.67]	211/24,102 [0.87]	104/165 [63]	141/204 [69]
NELSON N [%]	40/7289 [0.5]	57/7289* [0.8]	42/57 [73.7]	

NLST, National Lung Screening Trial; *, NELSON Round 2/3 data was presented together reflecting study design.

cancer screening. Data from California lung cancer registry also supports that degree of overdiagnosis is unlikely to be a major factor while defining the mortality benefit of lung cancer screening (21). Although overdiagnosis is an inevitable bias in screening studies, it can be mitigated with the advent of improving imaging modalities and precise definition of "positive result". At the same time, focus should be placed on minimizing risks with diagnostic and surgical interventions to develop a highly valuable and reliable screening service.

Stepping stones to adoption of LDCT as a screening tool

LDCT refers to using 10%~30% of the total radiation dose used in a standard non contrast CT scan. NLST used multi-detector CT scanners with an average estimated effective dose of 1.5 mSv average as compared to 5-7 mSv for standard CT (22). There has been a significant debate over adoption of LDCT as a screening tool. One of the major concerns is the risk of radiation induced cancer arising from LDCT itself and from subsequent imaging to work up the positive results. Regarding this issue, there was an important study that suggested that the risk of medical radiation exposure is considerably lower than the benefit of screening. Using the BEIR VII risk estimates, in an hypothetical screening scenario for an individual undergoing annual LDCT examination from age 55 to 74, the lifetime attributable risk (LAR) of lung cancer mortality resulting from radiation exposure is estimated to be 0.07% for males and 0.14% for females (23). To put this information in context, radiation exposure from natural and manmade sources can reach as high as 6.2 mSv per year and airline crew members are exposed to radiation levels as high as 2-6 mSv per year (24).

Since NLST, there have been continued improvements in LDCT technology and virtually all CT scanners in the United States can obtain LDCT scans at the doses used in the NLST or even lower. Ultra low dose CT scanners (ULDCT) techniques have been developed which deliver excellent images with less than 1 mSv exposure, which is comparable to radiation exposure by CXR. The efficacy of ULDCT was assessed in a study of 52 patients against traditional LDCT. ULDCT was found to have a true positive factor of 0.944 for nodules >4 mm in size, which is the current cut-off for reporting a positive result in screening cohort (25). Hence, with the continued technological advancements we can hope to achieve the same diagnostic accuracy with the least possible radiation exposure. These studies have been conducted in a population with normal BMI and the data needs to be extrapolated and validated in patients with higher BMIs as they comprise approximately more than one-third of current population of the USA (26).

Opportunities for rapid learning

NLST initially showed a 20% mortality benefit with LDCT screening as compared with CXR after three rounds of screening. Refinement of the approach to screening can potentially further improve this result. For example a re-analysis of NLST outcomes was conducted using an eligibility risk model constructed from PLCO case outcomes showed that they could define a higher risk cohort to use for the LDCT screening process (27). Two recent reports have suggested that sustained annual screening may reduce lung cancer mortality between 40% and 60% under different screening scenarios from analysis of the long term results of the New York Early Lung Cancer Action Project (NY-ELCAP) data (28,29). The benefits of LDCT screening are also promising from analysis of the preliminary data from NELSON trial as it show better stage I cancer detection rate compared to the NLST (*Table 2*), despite using different criteria for interpretation and diagnostic work up of a positive result (30). This demonstrates the scope for improvement in LDCT screening and the process of developing a good screening model.

Novel and promising principles for improving detection and diagnostic work up a nodule have been developed and

inculcated into trial protocols since the NLST trial. NLST is a valuable data resource allowing for improvement in screening process and comparative interpretation of the same. Rapid refinement of CT scan resolution and development of newer techniques such as ULDCT have resulted in early and reliable detection of stage I smaller primary lung cancer. Since most of the pulmonary nodules less than 1 cm in diameter are benign in setting of a screening test (31,32), various concepts of volumetric analysis of nodule detection and restricting diagnostic work up to nodules which show significant growth over time have been tested (33). NELSON study design used this interval-growth diagnostic work up resulting in a diagnostic sensitivity of 95% and a specificity of 99% for LDCT. The rate of invasive diagnostic work up was 12% in NELSON (8). This interval-growth criterion for suspicious nodules was also applied in a cohort of 4,700 screening patients and only 3% of the patients underwent invasive diagnostic work up and the rate of false positive detection was 0.42% (34). Another approach is to change the threshold of nodule size for detection which was included in I-ELCAP trial. Reducing the nodule size threshold from 4-5 to 7-8 mm significantly reduced the frequency of "false positive" lung cancers while maintaining the diagnostic accuracy (35). However, in raising the threshold for nodule size to 8 mm there would have been a delay of 9 months in 6% of the patients diagnosed with stage I lung cancer within 1 year of baseline screening in I-ELCAP.

New information also suggests it is useful to consider nodule characteristics such as ground glass, solid, non-solid and part solid during evaluation. It is known that only 20% of pure and 40% of part solid GGOs gradually grow over time with a doubling time of 600-900 and 300-450 days respectively (36). Fleischer society further recommends no additional surveillance work up for pure GGOs 5 mm diameter or less (37). NCCN has already incorporated the results from this study and has stratified the nature and intensity of follow up and diagnostic work up based on nodule size and interval growth (11). *Figure 1* shows the NCCN clinical practice guidelines in oncology (NCCN Guidelines®) for lung cancer screening, for work up of solid or part solid nodule found during screening evaluation.

At the time of NLST, surgical care protocols were not developed and minimally invasive surgery was still in the nascent stages. Minimally invasive technique involving sub lobar resection was analyzed in a retrospective review of 347 thoracic resections and long term (10 years) results of sublobar resection were equivalent to lobectomy in clinical stage IA cancers (38). These results favor detection of stage I cancers with screening and provide added benefit of preserving large amount of well-functioning tissue, hence lowering the post-operative morbidity.

All these advancements require an infrastructure to include rapid learning and implementation of the same to structure a highly efficacious and cost effective algorithm in lung cancer screening and its implementation as a public screening service. Using published approaches from the I-ELCAP experience, actuarial simulation models have reported this implementation to be cost effective. A cost benefit analysis in 2012 estimated the cost of screening for lung cancer to be $247 per person screened per annum assuming that 75% of screenings were repeat testing, which is in concordance with the data of a large collaborative study of low-dose spiral CT screening in population ages 50-55 (9,39). As well, in the setting of a commercial insurer, the incremental cost of providing LDCT service to a routine full medical coverage plan was estimated to be around $0.76 per member per month. By comparison, this cost was significantly lower than the insurer cost for breast, colorectal, or cervical cancer which was $2.50, $0.95, and $1.10 respectively (39). An older patient-level micro simulation study showed that annual screening of current and former smokers aged 50 to 74 years would cost between $154,000 and $207,000 (2012 USD) per quality-adjusted life year saved as compared to no intervention (40). However, Pyenson and co-workers using estimates of cost and outcomes from best current practice have predicted that with annual LDCT screening, 985,284 quality adjusted life years could be saved over the next 15 years (41).

NCCN (11) has emerged as a useful source of frequently updated lung cancer screening process information. They recommend the use of state-of-the-art infrastructure comprising sophisticated multi-detector CT scanners, analytical software, physicists and radiologists to perform testing at acceptable radiation exposures and use of standardized terminology for interpretation and appropriate guidelines to report the results. It also requires a reliable system to communicate with the screening subject and primary care physicians to ensure the tracking of screened individuals and documenting outcomes.

Implementation of LDCT screening can prove to act as a smoking cessation intervention itself. Twenty three percent of active smokers reported quitting after first annual round of screening in ELCAP trial (42), as against the background quit rate in general population of 4%. Further, with the addition of smoking cessation to that screening process, the cost utility ratio of quality adjusted life years could

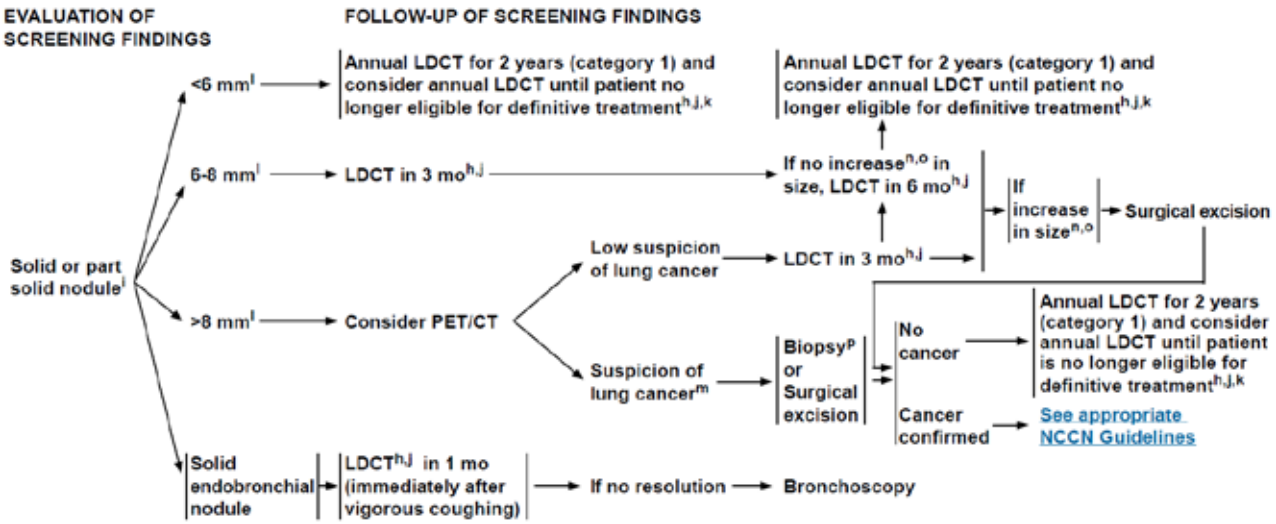

Figure 1 NCCN clinical practice guidelines in oncology (NCCN Guidelines®) for lung cancer screening, for work up of solid or part solid nodule found during screening evaluation. [h], all screening and follow-up CT scans should be performed at low dose (100-120 kVp & 40-60 mAs or less), unless evaluating mediastinal abnormalities or lymph nodes, where standard dose CT with IV contrast might be appropriate. There should be a systematic process for appropriate follow-up; [i], without benign pattern of calcification, fat in nodule as in hamartoma, or features suggesting inflammatory etiology. When multiple nodules are present and occult infection or inflammation is a possibility, an added option is a course of a broad-spectrum antibiotic with anaerobic coverage, followed by LDCT 1-2 months later; [j], if new nodule at annual or follow-up LDCT. New nodule is defined as ≥3 mm in mean diameter; [k], there is uncertainty about the appropriate duration of screening and the age at which screening is no longer appropriate; [l], mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter; [m], criteria for suspicion of malignancy: hypermetabolism higher than the background of surrounding lung parenchyma, regardless of absolute SUV; [n], for nodules <15 mm: increase in mean diameter ≥2 mm in any nodule or in the solid portion of a part solid nodule compared to baseline scan. For nodules ≥5 mm: increase in mean diameter of ≥15% compared to baseline scan; [o], rapid increase in size should raise suspicion of inflammatory etiology or malignancy other than non-small cell lung cancer; [p], tissue samples need to be adequate for both histology and malignancy testing. Travis WD, *et al*. Diagnosis of lung cancer in small biopsies and cytology: implications of the 2011 international Association for the study of lung cancer/American Thoracic Society/European Respiratory Society Classification. Arch Pathol Lab 2013;137:668-684.

be reduced from $28,240 to $16,198 per life year gained. Hence, apart from reducing medical costs, inclusion of smoking cessation interventions will help reduce mortality and morbidity more than the screening alone.

Conclusions

Despite promising results, the adoption of lung cancer screening has been slow. We now know that LDCT screening reduces mortality by allowing the more frequent diagnosis of lung cancer at an early stage. Furthermore, LDCT screening along with smoking cessation interventions is cost effective. LDCT as a screening modality has several robust features. It is painless, quick and easily available. The risk of radiation exposure associated with annual screening LDCT is often overstated and overestimated and is in fact low. This amount of radiation exposure in older, heavily tobacco-exposed populations, it should not deter the high risk populations from seeking screening testing. Overdiagnosis bias can be mitigated by the inclusion of case selection using serial LDCT scans to restrict diagnostic work-ups to individuals that demonstrate rapid pulmonary nodule growth. With the marked improvement in diagnostic evaluation of pulmonary nodule, more tailored and minimally invasive surgical techniques and improvements in LDCT technology, the case for adoption of lung cancer screening as a public health policy is stronger than ever. Under the Affordable Care Act all commercial insurers will provide LDCT to their beneficiaries and from a health equity perspective, a strong case exists for CMS to provide this cancer screening service soon as well. Thoughtful implementation of a high quality

new lung cancer screening service along with necessary measures for tracking outcomes is a national matter of urgent priority.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Implementing lung cancer screening in the real world: opportunity, challenges and solutions

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Abstract: The World Health Organization estimates that, in 2012, there were 1,589,925 deaths from lung cancer worldwide. Screening for lung cancer with low-dose computed tomography (LDCT) has the potential to significantly alter this statistic, by identifying lung cancers in earlier stages, enabling curative treatment. Challenges remain, however, in replicating the 20% mortality benefit demonstrated by the National Lung Screening Trial (NLST), in populations outside the confines of a research trial, not only in the US but around the world. We review the history of lung cancer screening, the current evidence for LDCT screening, and the key elements needed for a successful screening program.

Keywords: Lung cancer; lung cancer screening; computed tomography

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Lung cancer is a devastating disease, with the majority of patients diagnosed in advanced stages, resulting in an overall 5-year survival of only 18% (1). National Cancer Institute (NCI) data for non-small cell lung cancer in the United States (US) for the period from 2005 through 2011 showed that only 16% of lung cancers are diagnosed at a localized stage, and the majority, 57%, is diagnosed with distant disease (2). The goal of screening for lung cancer is to reduce lung cancer mortality by increasing the number of cases diagnosed at a localized stage, thereby allowing a curative approach to treatment. In 2011, the largest randomized controlled trial of CT screening for lung cancer to date, the National Lung Screening Trial (NLST), changed the face of early detection of lung cancer when it reported a 20% reduction in lung-cancer specific mortality in a high- risk cohort of patients screened in the US with CT in comparison with the control arm of high-risk individuals screened with annual chest radiographs (CXR) for 3 years (3). In contrast to symptom-detected lung cancers, the majority (63%) of CT-screen-detected lung cancers was Stage I, and only 12.8% with a positive screen had distant disease. The optimistic approach to these results is that CT screening could shift the lung cancer population from one dominated by advanced, incurable disease to a population with a high percentage of early stage, resectable disease. On the other hand, it is yet to be shown if the NLST results can be generalized either to the community setting within the US or to countries outside the US (4). In this article, we will explore the issues driving the lung cancer screening debate.

Prior attempts at lung cancer screening

In the 1970s, there was a large scale effort, funded by the NCI, to examine the role of sputum cytology in addition to chest radiography in screening for lung cancer. Three institutions, the Mayo Clinic in Rochester, Minnesota, the Johns Hopkins Medical Institution in Baltimore,

Maryland, and the Memorial Sloan-Kettering Cancer Center (MSKCC) in New York City accrued approximately 30,000 adult male smokers (5-8). The trial designs at Johns Hopkins and MSKCC were identical—patients were randomized to either a single screen (CXR annually) or a dual screen (CXR annually, sputum cytology every 4 months). This trial design specifically addressed the role of sputum cytology as all participants underwent annual CXR screening, and eventually determined that there was no mortality benefit from the addition of sputum cytology. In the Mayo Lung Project (MLP), participants were randomized to an experimental arm in which participants were offered (and encouraged) free CXR and free sputum cytology to be obtained every 4 months, or to a control arm in which participants were simply advised to undergo these tests annually (9). The early results were encouraging. After 6 years, there were more lung cancers diagnosed in the screened group, and the screen-detected lung cancers were more likely to be resectable, and in Stage I or II, in comparison with a group of clinical cases of lung cancer seen at the Mayo Clinic (7). There were, however, slightly more lung cancer deaths in the experimental arm than in the control arm, and consequently no reduction in lung cancer mortality with CXR screening (10).

In 1993, the NCI initiated the Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening trial to determine if screening could reduce mortality from these four cancers (11). The design of the lung component of the PLCO differed from the earlier NCI trials in several areas: (i) it included women and never-smokers; (ii) the control arm did not include a CXR; and (iii) the sample size was much larger. A total of 154,934 participants were enrolled between 1993 and 2001. After 13 years of follow-up, it was reported that screening with CXR did not reduce lung-cancer specific mortality (12). There were 1,213 lung cancer deaths in the CXR-screened group and 1,230 lung cancer deaths in the control group, for a relative risk of lung cancer mortality of 0.99 (95% CI, 0.87-1.22). In a subset of participants who also met NLST eligibility criteria, the relative risk of lung cancer mortality in the CXR arm over the same 6-year follow-up period was 0.94 (95% CI, 0.81-1.10).

The introduction of CT screening

As CT technology evolved from single slice scanners to multi-slice scanners, the thorax could now be imaged with high spatial resolution in a single breath-hold (13). This technological advance spurred a renewed interest in imaging-based lung cancer screening. In the early 1990s, single-arm trials of low-dose CT screening for lung cancer began in Japan and in the US. Masahiro Kaneko and his colleagues at the National Cancer Center Hospital in Japan performed low-dose spiral CT for the purposes of lung cancer screening in 1,369 individuals, between September 1993 and April 1995 (14). They identified 15 peripheral lung cancers, 14 of which were Stage I, and 11 of which were missed on CXR. Simultaneously, Claudia Henschke and her colleagues at Cornell and New York University initiated the Early Lung Cancer Action Project (ELCAP), scanning 1,000 individuals who were ages 60 and older, with at least a 10 pack-year smoking history (15). In the nodules identified at CT, 27 proved to be malignant, and 23 of those were Stage I disease. They also diagnosed malignancy in four additional participants, two with endobronchial disease and two with mediastinal disease. As in Japan, many (20 of 27) nodules representing lung cancer were not detected by CXR.

These single-arm trials suggested that low-dose CT screening for lung cancer might achieve what CXR screening had not, not only a stage shift towards earlier, resectable disease, but also a reduction in lung cancer mortality. Proving that would require randomized controlled trials.

The National Lung Screening Trial (NLST)

The NLST opened in the US in 2002, enrolling 53,454 participants between September 2002 and April 2004. Eligibility criteria included ages 55 to 74, and current or former (quit within the last 15 years) smoker with at least 30 pack-year smoking history. Exclusion criteria included a history of lung cancer, treatment for any prior malignancy other than non-melanoma skin cancer within the last 5 years, present symptoms suggestive of lung cancer, requirement for home oxygen supplementation, and any medical condition that would pose a significant risk of mortality within the proposed 8-year trial period. The experimental arm received screening with low-dose CT annually for 3 years, and the control arm received screening with single view CXR. Although the control arm would have ideally been no screening (standard of care), including the CXR in the control arm facilitated accrual and retention, and the concurrently running PLCO trial would allow comparison between three arms—the CT arm, the CXR arm, and no screening.

In 2011, the NLST reported a 20% reduction in lung cancer mortality in heavy smokers screened with three annual low-dose computed tomography (LDCT) scans

relative to those screened with three annual single view CXR (3). This was a milestone not only for lung cancer screening, as the first randomized controlled trial to demonstrate this benefit, but also for the diagnosis and treatment of lung cancer in general. The results have been met with cautious optimism, however, as it has become clear that the 20% mortality reduction was in a highly selected cohort, following a specific protocol, predominantly at large academic institutions.

European randomized lung cancer screening trials

In 2010, the principal investigators of the six on-going European randomized controlled trials of lung cancer screening and of the one trial in preparation in the United Kingdom began to pool information regarding the epidemiological, radiological, and nodule management aspects of their trials, creating the European Randomized Lung Cancer CT Screening Trials (EUCT) (16). These trials included the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) (17), the Danish Lung Cancer Screening Trial (DLCST) (18), the Multi-centric Italian Lung Detection Trial (MILD) (19), the Italian Lung cancer Computed Tomography screening trial (ITALUNG) (20), the Detection and screening of early lung cancer by Novel imaging TEchnology and molecular assays (DANTE) (21), the German Lung Cancer Screening Intervention Study (LUSI) (22), and the United Kingdom Lung Cancer Screening Trial (UKLS) (23).

Although there are slight variations in the individual study designs, all seven trials have a control arm of no screening, and inclusion criteria of heavy current or former smokers. The number of screening rounds varied, from one (UKLS) to ten (MILD); the screening interval ranged from 1 to 2.5 years; three-dimensional volume measurement was included in most trials, but two-dimensional nodule measurements only were utilized in two (DANTE, ITALUNG) (24). The lower age limit was 50 in most trials, with the exception of ITALUNG and DANTE, with lower age limits of 55 and 60, respectively.

The combined EUCT trials have a higher percentage of male participants than the NLST, in which 59% of the participants were male (25). In the largest EUCT trial, the NELSON trial, with 15,822 participants, 84% were male. Of the six EUCT trials with completed enrollment, 25,902 of 34,094 (76%) participants were male. The higher percentage of male participants in the EUCT has potential implications for the reduction of lung cancer mortality. In the NLST, Pinsky *et al*. calculated the overall lung cancer mortality risk ratio (RR), defined as the lung cancer death rate in the CT versus CXR arms, at 0.84 (95% CI, 0.75-0.95). There was a slight difference in the RR for women versus men, however, with a greater reduction in lung cancer mortality risk in women (RR of 0.73 *vs*. 0.92) (26). If this sex-linked difference in mortality is also seen in the EUCT, the overall mortality reduction would be impacted by a greater percentage of male participants.

The UKLS, with its planned enrollment of 32,000 individuals, could ultimately dominate the profile of the EUCT participants. The UKLS uses the Liverpool Lung Project (LLP) risk prediction model (27) to determine an individual's lung cancer risk, and only those with at least a 5% risk of developing lung cancer within the next 5 years are invited to participate in the trial (23,27). In the first recruitment phase of the trial, men responding to the recruitment questionnaire were more than twice as likely as women to be considered high risk by the LLP model; 2,016 (17%) of male and 832(7%) of female positive responders were deemed high risk (28).

Potential impact of screening on stage distribution and mortality

When a patient first begins a CT screening program for lung cancer, a diagnosed lung cancer may be in advanced stages even though the patient is asymptomatic. A better estimate of the potential for CT screening to generate a stage shift in lung cancer is the percentage of lung cancers in early stages at subsequent annual screens. In the CT arm of the NLST, 87/183 (47.5%) of lung cancers were stage IA and 57/183 (31.1%) were stage III or IV in the low-dose CT group at the second annual (T1) screen, among lung cancers of known stage (29). In comparison with the initial T0 screen the percentage of stage IA lung cancers was slightly higher, and the percentage of Stage III lung cancers was slightly lower (30) (*Table 1*). This was also observed in the NELSON trial, with 74.1% of lung cancers in stage IA in the second screening round and 64.9% in stage IA at the third screening round, as compared with 59.5% of lung cancers in stage IA in the first screening round (31). Although a stage shift suggests that screening will identify more surgically resectable cancers, it is not a substitute for the true measure of screening efficacy, which is a reduction in lung cancer mortality in comparison with a control arm.

Lung cancer screening has the potential to impact lung cancer mortality on a global level. The World Health

Table 1 Stages of lung cancers in the CT arm of the NLST, according to screening round, and as compared with SEER data (29,30)

	IA (%)	IB (%)	IIA (%)	IIB (%)	IIIA (%)	IIIB (%)	IV (%)
T0 (NLST)	45.8	9.0	3.5	4.2	11.8	10.4	15.3
T1 (NLST)	47.5	11.5	6.0	3.8	7.7	10.4	13.1
T2 (NLST)	50.4	13.5	3.5	2.2	6.5	8.7	15.2
SEER data	15% localized	15% localized	15% localized	22% regional	22% regional	22% regional	57% metastatic

NLST, National Lung Screening Trial; SEER, Surveillance, Epidemiology, and End Results.

Organization estimates that there were 1,824,701 new cases and 1,589,925 deaths from lung cancer worldwide in 2012 (32). If all those lung cancers could be identified through screening, a 20% reduction in lung cancer mortality could mean 317,985 fewer deaths from lung cancer worldwide each year. Many of those cancers occur, however, in individuals who do not meet current eligibility criteria for lung cancer screening, either because of age or smoking history. If the NLST eligibility criteria (age 55-74, at least 30 pack-year smoking history, former smokers quit within the last 15 years) were applied to the US population, only 26.7% of lung cancers would be identified (33). One of the reasons for this relatively low percentage of clinical cases of lung cancer is the age criterion: only 53.3% of cases of lung cancer in the US occur in patients 55 to 74; 27.6% of all lung cancers in the US occur in individuals 75 to 84 years old and an additional 8.4% are in the age group 45 to 54 (2). If the NLST eligibility criteria were revised to include age 50-79 and a 30+ pack-year history (any quit status), 46.3% of lung cancers would be included, but the percentage of the US population that would be eligible for screening would double, from 6.2% of the population over age 40 to 12.1%.

The NLST eligibility criterion of 30 pack-years, which reflects the total cigarette smoking exposure, does not distinguish between those who have smoked fewer cigarettes per day (smoking intensity) or a greater number of cigarettes over a shorter duration. It has been estimated that total exposure from smoking fewer cigarettes for a longer period of time is more deleterious than the equivalent exposure from smoking a greater number of cigarettes for a shorter period of time (34). Notably, the NCCN lung cancer screening guidelines currently include smokers with 20 pack-years and one additional risk factor as a second high-risk population for lung cancer (35).

Exclusion of former smokers who have quit for longer than 15 years contributes to a missed opportunity for early identification of lung cancer. We now know from PLCO data that, in individuals with a 30+ pack-year smoking history, the hazard ratio for lung cancer in former smokers relative to nonsmokers drops from 30.8 in individuals quit less than 5 years, to 14.8 in those quit 10 to 15 years (36). However the lung cancer risk remains high after 15 years of quitting, with hazard ratios of 13.5 and 9.9 in former smokers with 15 to 20 years, and 20 to 25 years quit time, respectively.

Who should be screened?

Optimizing the target population for lung cancer screening has tremendous significance, not only for the individual who weighs the risks and benefits of screening, but also for health care providers, health insurers and governments who must consider the fiscal impact of implementing lung cancer screening. With data from the NLST and the PLCO trials, de Koning *et al*. used computer modeling to estimate the benefits (lung cancer deaths averted, life-years gained) and harms (CT examinations, false-positive results, overdiagnosed cases, and radiation-related deaths) of lung cancer screening with varying eligibility criteria and screening intervals (37). They concluded that the most advantageous strategy was annual CT screening from ages 55 through 80 years for ever-smokers with a smoking history of at least 30 pack-years and ex-smokers with less than 15 years since quitting. The calculated benefits and harms of this screening strategy in a 100,000 person cohort are presented in *Table 2*.

McMahon *et al*. reported similar eligibility criteria for lung cancer screening efficiency. They defined the most efficient screening strategy as the one with the greatest number of lung cancer deaths averted for each possible number of CT screens (38). Using five separate microsimulation models, they determined that the most efficient models included an average starting age of 55 years, a stopping age of 80 or 85 years, an average minimum pack-years of 27, and the maximum time since quitting of 20 years. Annual screening in a population of individuals 55 to 85 years old, with a

Table 2 The calculated benefits and harms of annual CT screening from ages 55 through 80 years for ever-smokers with a smoking history of at least 30 pack-years and less than 15 years since quitting in a 100,000 person cohort (37)

LC detected in stage I/II	NNS (per LC death averted)	Reduction in LC mortality	LC deaths averted (per 100,000 member cohort)	Life-years gained (per 100,000 member cohort)	FP test results	Biopsies or surgeries for benign lesions	Overdiagnosed cases of LC
50%	575	14% (range, 8.2%~23.5%)	497	5,250	67,550	910	190 (3.7% of all LCs)

LC, lung cancer; NNS, number needed to screen; FP, false positive.

≥30 pack year smoking history, and fewer than 20 years since quitting yielded 593 lung cancer deaths avoided (per 100,000 population), with a number needed to screen of 44 per lung cancer death avoided, and 6,237 life-years saved. There was a consensus among models that, compared with the NLST eligibility criteria, continuing screening to older ages was more efficient than stopping at age 75, but initiating screening at younger ages (e.g., 45) was less efficient. Biennial screening and increasing the minimum pack-years (e.g., 40) provided fewer benefits.

Cost-effectiveness of lung cancer screening

For many years, estimates of the cost-effectiveness of CT screening for lung cancer were based on modeling, as limited data was available for real world analysis. These estimates varied widely, ranging from $2,500 (39) to $23,100 (40) per life-year saved for one-time screening, and $116,300 (current smokers) to $2,322,700 (former smokers) per quality-adjusted life-year (QALY) gained for a 20-year screening program (41). Current estimates continue to vary, especially in countries with differing models of health care delivery.

Using baseline results from ELCAP, Marshall *et al.* estimated that, in the US, a one-time screen was cost-effective in a very high-risk cohort of patients 60 to 74 years of age with a lung cancer prevalence of 2.7%, with a cost of US$5,940 per life year saved (based on 1999 reimbursement rates) (40). Even in a lower risk general population with a lung cancer prevalence of 0.7%, they determined that a one-time screen was cost-effective at US$23,100 per life year. They extended this analysis, in the same high-risk cohort, to annual screening for 5 years and determined that screening remained cost-effective, under optimal conditions, at approximately $19,000 per life year saved (42). Wisnivesky *et al.* also used ELCAP baseline screening data in a decision analysis model comparing low-dose CT scan screening of high-risk individuals (age >60 years, ≥10 pack-years of cigarette smoking) to observation without screening (39). They estimated that the incremental cost-effectiveness ratio (ICER) of a single screen was $2,500 per life year saved.

The costs per QALY gained were estimated to be much higher, in a computer-simulated model of 100,000 current, quitting, and former heavy smokers over a 20-year period, assuming a 50% stage shift and a 13% lung cancer mortality reduction (41). In this model, Mahadevia *et al.* estimated that the costs per QALY gained were $116,300 for current smokers, $558,600 for smokers who quit at the time of the screen, and $2,322,700 for smokers with a 5-year quit time. McMahon *et al.* implemented a patient-level microsimulation model (Lung Cancer Policy Model) to estimate the cost-effectiveness of lung cancer screening in six US cohorts (men and women, aged 50, 60 and 70 years), using survey data to attribute smoking histories to the cohorts (43). They determined that annual CT screening in individuals with ≥20 pack-years smoking history reduced lung cancer-specific mortality by approximately 18% to 25% at 10 years, at a cost of $126,000 to $169,000 per QALY gained.

Following the release of the NLST mortality data, cost-effectiveness analyses could now incorporate more specific data for lung cancer mortality reduction, diagnostic procedures and lung-cancer treatment. Within the American College of Radiology Imaging Network (ACRIN) arm of the NLST, detailed information was collected regarding health-related quality-of-life, diagnostic procedures performed, lung cancer staging and treatment. Black *et al.* calculated an incremental cost effectiveness ratio (ICER), which is the ratio of the incremental cost of screening to the incremental health benefit, of US$81,000 per QALY gained (95% CI, $52,000 to $186,000) in the CT-screened arm of the NLST, compared with no screening (44,45). There was a wide variation in ICERs in various subgroups, with lower ICERs in women ($46,000/

QALY in women *vs*. $147,000/QALY in men), in current smokers ($43,000/QALY in current smokers *vs*. $615,000/QALY in former smokers), in the 60-69 years old age group ($48,000 to $52,000/QALY), and in individuals in the two highest risk quintiles ($32,000 and $52,000/QALY). These results highlight the opportunity to better refine selection criteria for screening, not only to maximize patient benefit and minimize patient risk, but to also provide a health service that is cost-effective. In this regard, extending eligibility criteria beyond age and smoking history may be of value.

Risk stratification

The NLST and NELSON trial designs incorporated the two most significant predictors of lung cancer risk: age and smoking history. Current recommendations for screening have followed suit, with slight variations in ages and pack-years for eligibility. It is possible, though, that with better risk prediction, screening could be more efficient, with more lung cancers diagnosed, and fewer individuals screened. The age and smoking history criteria that currently determine screening eligibility yield a population with widely varying risks of lung cancer. Kovalchik *et al*. stratified the NLST participants into five quintiles, according to the 5-year risk of lung cancer death, ranging from the lowest risk (0.15% to 0.55%) to the highest (more than 2.0%) (46). Within the CT arm, across all quintiles, there were 1,083 lung cancer cases, of which 530 (48.9%) were Stage I. When this data is broken down by risk quintile, it becomes apparent that there was only one lung cancer death prevented in the lowest risk quintile. The majority (88%) of screen-prevented lung cancer deaths were within the three highest risk quintiles. A screening program that selected only the 60% of patients in the higher risk groups would reduce the number needed to screen (NNS) to prevent one lung cancer death from 302 to 161, and would reduce the number of false positives per CT-prevented lung cancer death from 108 to 65. This would have a significant impact on the costs of lung cancer screening, not only in terms of financial costs, but in terms of patient risks. On the other hand, this approach would miss 16.2% (176/1,082) of lung cancer cases, and 12.5% (11/88) of preventable lung cancer deaths.

Tammemägi *et al*. developed a logistic regression lung cancer risk prediction model based on the 6-year incidence of lung cancer in smokers in the control arm of the PLCO trial (47). The model includes four smoking variables [smoking status (current/former), number of cigarettes smoked per day, duration of smoking (years), and quit time (years)] and seven non-smoking variables (age, education level, body mass index, history of COPD/emphysema/chronic bronchitis, personal history of cancer, family history of lung cancer, race and ethnicity). This model is the basis for an on-line calculator (48) that allows individuals to determine their likelihood of developing lung cancer within the next 6 years, after entering the personal data described above. Health care providers can use risk prediction calculations such as these, within a shared decision making session, to counsel patients on their individual lung cancer risks, and the advisability of lung cancer screening.

False positive screens

The NLST protocol defined a mean nodule diameter of 4 mm or greater as a positive screen. As a result, there was a high rate of false positive screens in both the LDCT and the CXR groups (96.4% and 94.5%). Further analysis of NLST and ELCAP data suggest that the number of false positive screens can be reduced without significantly impacting sensitivity by using larger nodule diameter thresholds (49,50). Currently, the NCCN and ACR guidelines define a positive screen as a nodule with a mean diameter of 6 mm or larger (35,51). If this threshold had been applied in the International ELCAP, there would have been a 36% decrease in diagnostic work-ups and no delayed diagnoses of lung cancer (49). Applying a 6 mm threshold to the NLST data avoids 37% of the false positives, but there would be a delay in the diagnosis of 3% of the lung cancer cases (50).

The NELSON trial design also reduces the number of screens considered false positive, by using three-dimensional volume measurements rather than the mean nodule diameters used in earlier trials. The NELSON trial added a third "indeterminate" category of scan results to the standard "positive" and "negative" categories. These three categories of screening results were based on nodule volume measurements, and defined as (I) positive: non-calcified nodule with a solid component more than 500 mm^3 in volume (equivalent to >9.8 mm in diameter); (II) indeterminate: volume of the largest solid nodule or of the solid component of a part-solid nodule of 50 to 500 mm^3 (4.6 to 9.8 mm in diameter) or the diameter of a nonsolid nodule greater than 8 mm and (III) negative. Patients with indeterminate screens underwent a 3-month follow-up CT. If there was no significant growth on the follow-up CT, the screen was considered to be negative and the patient was rescheduled for an annual repeat CT in 9 months. Nodule growth was measured as Volume Doubling

Time (VDT), which was divided into three categories: >600 days, 400-600 days, and <400 days (52). This two-step approach to nodules 50 to 500 mm^3 in volume significantly reduced the number of false positive screens, returning the majority of patients to an annual screening regimen after only a 3-month delay.

Risk stratification can also occur at the nodule level. Just as risk stratification can determine an individual's likelihood of malignancy, risk stratification can assist in determining the likelihood that a nodule identified on a screening CT is malignant. The use of these nodule-oriented risk prediction models can further minimize the harms of false positive findings by reducing the number of unnecessary diagnostic and invasive procedures. In 1997, Swensen *et al.* published a prediction model for indeterminate nodules that incorporated three clinical characteristics (patient age, smoking status, history of cancer) and three nodule characteristics (diameter, spiculation, upper lobe location) (53). More recent models have expanded this concept to include nodule volumes (54). Horeweg *et al*. reported that the NELSON nodule management protocols based on nodule volumes and volume doubling times described above (55) outperformed the American College of Chest Physicians (ACCP) nodule management guidelines (56), which are based on the diameter-specific Fleischner Society recommendations (57).

Establishing a clinical screening program

A successful screening program outside of a clinical trial requires robust resources and significant buy-in from a variety of stakeholders. The initial stage of program inception demands close collaboration between administrative and clinical staff. Preliminary meetings should include specialists in thoracic radiology, thoracic oncology, pulmonology, and thoracic surgery. If desired, interventional radiology and pulmonary pathology may participate as well. One or more of these specialists should be designated as a medical director or physician champion of the program. Other key participants in program construction include hospital administration, business management, nursing, and marketing personnel. Active participation from all of these stakeholders is required for initial startup and ultimate success.

Patient recruitment into the program is the fuel which feeds a sustained effort. An effective marketing strategy is required to reach health care providers and patients alike. For instance, educational resources can be offered to primary care providers and physician extenders who encounter significant numbers of potentially eligible patients. These resources should form the basis for a shared decision making process, and clearly delineate eligibility criteria, benefits and risks of screening. Educational resources may be in the form of pamphlets, e-mail brochures, one-on-one office visits, grand rounds, and after-hours seminars. Follow-up phone calls may address key questions from these providers. An effective marketing strategy may include direct marketing to at-risk patient populations. Print media, broadcast media, internet, office pamphlets and posters can all play a role in reaching middle-aged and older smokers. The program's marketers should receive feedback from enrolled patients to determine the effectiveness of these marketing strategies, in order to tailor and refine these techniques.

Smooth operation of a clinical screening program will require a multifaceted effort. Prior to scheduling an exam, appropriate personnel must screen each patient to determine eligibility, and assure that shared decision making takes place with an appropriate clinical provider (58). Hospital administration and/or business personnel should oversee patient scheduling, registration, and payment. In the US, some programs offer services on a cash basis, but since the advent of the US Preventive Services Task Force (USPSTF) certification (59) and Centers for Medicare and Medicaid Services (CMS) approval (58), third party payment in the US has become more common. Precertification may or may not be necessary depending on the payer. Image acquisition requires a CT scanner capable of performing a single-breath-hold low-dose screening protocol, typically 16-channel or beyond. Although the scan protocols are straightforward, technologists with special registry in CT are necessary to provide consistent, high-quality scans with appropriate post-processing. Most programs utilize thoracic trained radiologists for image interpretation and reporting, although this function may also be performed by other radiologists with documented experience in chest CT (60). Images are transmitted to a picture archiving and communication system (PACS) which allow display for interpretation, archival, and accessibility to referring clinicians if desired.

Recent efforts by organized leadership in thoracic radiology have developed a structured reporting system analogous to commonly used mammography reporting (51). This "Lung-RADS™" system provides a common set of follow-up guidelines for nodules of certain levels of suspicion. It is critical that all members of the clinical team understand the meaning of the Lung-RADS™ categories so that appropriate follow-up care can be predictable and effective (*Table 3*) (51,61).

Table 3 Lung-RADS™ Version 1.0 Assessment Categories (51). Not shown in this table is category 0, incomplete, for which additional imaging or comparison with prior imaging is needed

Category	Descriptor	Category	Findings	Management	Probability of malignancy	Estimated population prevalence
Negative	No nodules and definitely benign nodules	1	No nodules Nodules with benign pattern of calcification or fat attenuation	Continue annual screening with LDCT in 12 months	<1%	90% (categories 1 and 2 combined)
Benign appearance or behavior	Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	Solid/part solid <6 mm or new <4 mm Nonsolid <20 mm or ≥20 mm and unchanged or slowly growing Category 3 or 4 nodules unchanged for ≥3 months		<1%	
Probably benign	Probably benign findings for which short term follow-up is suggested	3	Solid ≥6 to <8 mm or new 4 mm to <6 mm Part solid ≥6 mm with solid component <6 mm or new <6 mm Nonsolid ≥20 mm	6 months LDCT	1%~2%	5%
Suspicious	Findings for which additional diagnostic testing or tissue sampling is recommended	4a	Solid ≥8 mm to <15 mm or growing <8 mm or new 6 to <8 mm Part solid ≥8 with solid component ≥6 to <8 mm, or with new or growing <4 mm solid component Endobronchial nodule	3 months LDCT; PET/CT may be used when there is a ≥8 mm solid component	5%~15%	2%
		4b	Solid ≥15 mm or new or growing and ≥8 mm Part solid with solid component ≥8 mm or with new or growing ≥4 mm solid component	Chest CT; PET/CT (if there is a ≥8 mm solid component) and or tissue sampling, depending on probability of malignancy and comorbidities	>15%	2%
		4x	Category 3 or 4 nodules with additional features that increase the suspicion of malignancy			

LDCT, low-dose computed tomography.

Successful centers typically enlist a core group of providers, often as part of a multi-disciplinary thoracic clinic, who manage data collected within the screening program. A nurse navigator is a crucial member of the clinic team. The navigator can be responsible for CMS-mandated patient risk counseling and shared/informed decision-making prior to the procedure, as well as smoking cessation counseling prior to and subsequent to the procedure (62). Weekly conferences can assist in discussing management of cases requiring intervention or close follow-up (e.g., Lung-RADS™ 3 & 4.) These management discussions are often part of a weekly multidisciplinary thoracic conference including members of thoracic surgery, pulmonary medicine, thoracic oncology, thoracic radiology, pathology, and radiation oncology.

Robust data collection is mandatory for a successful screening program. Local databases should include appropriate patient demographics (usually available through radiology/hospital information systems), exam results, follow-up recommendations, pathology results, and significant extrapulmonary findings. Structured reporting (e.g., Lung-RADS™) improves the meaningfulness of such

data. From this data the team may analyze positive screen rates, false-positive rates, and outcomes. Data may also be used to provide timely reminders for follow-up. In addition, CMS rules mandate that screening programs participate in an approved lung cancer screening registry (58).

The financial resources required to establish a lung cancer screening program are not small. Some of the key expenses involved include clinic space, salaries of administrative personnel, professional services, marketing teams, and employees. In the US, typical direct reimbursements for lung cancer screening include Medicare Part B (approved in February 2015), third party commercial insurance (mandated by the Affordable Care Act due to USPSTF recommendations), donations, grants, and occasionally direct cash payments from screened patients. Many screening programs will find that these direct reimbursement sources do not cover the entire cost of the program, and that reimbursement for "downstream" events such as follow-up diagnostic testing or surgical procedures may make up for such shortfalls.

Despite excellent planning and execution of a lung cancer screening program, multiple challenges remain. Primary care clinicians may feel that their patients are candidates for screening, and wish to refer them, but fear relinquishing control of the patient's care to the multidisciplinary team. While it is key that the multidisciplinary team supervise and control the screening process and data collection, primary care providers should be welcomed to participate with the multidisciplinary team when their patients are discussed.

The CMS-mandated shared decision making process can be time intensive for the nurse coordinator or referring primary care physician. Not uncommonly, patients will present for screening but do not meet accepted eligibility criteria. Program leaders should have established policies on whether they wish to screen self-paying patients not meeting eligibility criteria, as this can present an ethical challenge. These patients should still be offered counseling regarding smoking cessation.

Fail-safe mechanisms need to be in place to assure that timely results are communicated to the patient and referring provider. Additionally, similar mechanisms must assure that appropriate follow-up exams or procedures are scheduled in a timely manner. Accurate patient contact data (e.g., phone number, home address, email address) are crucial to prevent patients from "slipping through the cracks". Hospital or clinic information systems may have methods to provide automated patient reminders for follow-up screening, and can be helpful. During all patient contacts, the nurse coordinator must often coach patients on the importance of adherence to follow-up recommendations.

As has been the case with other types of screening over the past several decades, the growth and effectiveness of a population screening strategy is often heavily reliant on appropriately adequate reimbursements to allow the healthy sustenance of a screening program. Not surprisingly, third party payers often look to cost-effectiveness models to justify inclusion of a screening procedure in their covered benefits. Early analyses of lung cancer screening indeed seem to support its cost-effectiveness (44,63).

Future directions for lung cancer screening

As we move forward from the research domain into clinical application, guidelines for screening for lung cancer should continue to incorporate emerging data. Risk stratification calculations can refine patient eligibility criteria so that we optimize the diagnostic yield of CT screening. This will hopefully help identify lung cancers in patients who do not meet current eligibility criteria, as well as limit screening in patients who are currently eligible but at lower risk. Techniques that offer even lower radiation doses could be mandated. The risks of screening can be further reduced by using nodule risk predictors, including measuring nodule volumes and growth rates, to reduce the number of follow-up examinations and invasive procedures. Structured reporting systems such as Lung-RADS™ should undergo continual evaluation and modification. Finally, we must collect the data from clinical screening programs to ensure that CT screening for lung cancer continues to provide a cost-effective mortality benefit in specific populations, regions, or age groups.

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Footnote

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Screening for lung cancer using low-dose computed tomography: concerns about the application in low-risk individuals

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Abstract: Low-dose computed tomography (LDCT) has been increasingly accepted as an efficient screening method for high-risk individuals to reduce lung cancer mortality. However, there remains a gap of knowledge in the practical implementation of screening on a larger scale, especially for low-risk individuals. The aim of this study is to initiate discussion through an evidence-based analysis and provide valuable suggestions on LDCT screening for lung cancer in clinical practice. Among previously published randomized controlled trials (RCTs), the National Lung Screening Trial (NLST) is the only one demonstrating positive results in a high-risk population of old age and heavy smokers. It is also shown that the potential harms include false-positive findings, radiation exposure etc., but its magnitude is uncertain. In the meantime, the current risk stratification system is inadequate, and is difficult to define selection criteria. Thus, the efficacy of LDCT in lung cancer screening needs to be confirmed in future trials, and the procedure should not be proposed to individuals without comparable risk to those in the NLST. Furthermore, there is a lack of evidence to support the expansion of LDCT screening to low-risk individuals. Therefore, recommendation of LDCT screening for these patients could be premature in clinical practice although some of them might be missed based on current definition of risk factors. Further studies and advances in risk assessment tools are urgently needed to address the concerns about lung cancer screening in order to improve the outcomes of lung cancer.

Keywords: Lung neoplasm; risk; screening; spiral computed tomography

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Introduction

Lung cancer is the leading cause of cancer mortality, accounting for approximately 28% of all cancer-related deaths (1). The current estimate suggests that approximately 7% of the population born today will be diagnosed with lung cancer in their lifetime, and approximately 6% will die of it (SEER Cancer Statistics Review, 2014). According to GLOBOCAN 2012, 35.78% of all newly diagnosed lung cancer cases and 37.56% deaths of lung cancer occur in China. Moreover, the disease is projected to be the sixth leading cause of death worldwide and the third in high-income countries in 2030 (2). Thus, it is a major public health problem.

Despite the development of new therapeutic agents and technologies, the 5-year survival rate of 6% to 18% for lung cancer (3) has not improved significantly over the past 20 years (4). Nevertheless, when the disease is diagnosed at an early stage, its 5-year survival rate is up to 67% (5). However, only 16% of lung cancer patients are diagnosed at early stages (1), whereas 61% of women with breast cancer and 91% of men with prostate cancer are diagnosed at early stage, owing to improvements in early detection and treatment. Consequently, the mortality rates for breast and prostate cancers have decreased from their peaks by 34% and 45%, respectively (1). Therefore, reliable detection and treatment of lung cancer in its earlier stages is a promising approach to improving the prognosis of lung cancer.

Screening for lung cancer dates back to 1968 in the United Kingdom, and several screening methods were tried, including chest X-ray (CXR), CXR with sputum cytology, serum biomarker testing, and fiber optic examination of the bronchial passages. However, these methods yielded limited efficacy in survival improvement, possible owing to the disease's clinical and pathologic heterogeneity (6). In 2011, the initial results of the National Lung Screening Trial (NLST) (7) were published, reporting a relative 20% reduction in lung cancer-specific deaths among high-risk participants undergoing low-dose computed tomography (LDCT) compared to those receiving CXR. The acquisition variables of LDCT were chosen to reduce exposure to an average effective dose of 1.5 mSv. The criteria for high-risk participants of the NLST included patients aged between 55 to 74 years, those currently smoking 30 pack-year, or former smokers who quit within the past 15 years.

The NLST trial was acclaimed as a major breakthrough in lung cancer screening. As a result, lung cancer screening using LDCT was recommended by various organizations, including the American Association of Thoracic Surgery (8,9), American College of Chest Physicians, American Society of Clinical Oncology, American Thoracic Society (10), National Comprehensive Cancer Network, American Lung Association, American Cancer Society (11), and the United States Preventive Services Task Force. Although a major push for primary care providers to incorporate lung cancer screening using LDCT into their practices is expected, clinicians inevitably encounter patients who are interested in screening but do not meet the previously described high-risk criteria. Thus, the question remains whether it is rational to screen as many people as quickly as possible or how these screening candidates should be wisely selected. As it is uncertain if people who do not meet the NLST inclusion criteria have a low risk of developing lung cancer and whether they benefit from screening, the potential harms associated with the procedure and its balance among cost, risks, and benefits should be carefully considered. In the present article, we systematically review the practical aspects of lung cancer screening using LDCT to provide an evidence-based analysis for whether LDCT screening should be expanded to the low-risk population.

Is there sufficient evidence to support lung cancer screening using LDCT?

We conducted a systematic review of current literature on the harms and benefits of lung cancer screening using LDCT and found 107 relevant clinical trials. Mass lung cancer screening programs using CT have been active since the mid-nineties in Japan (12-14), and many uncontrolled studies were launched during the following years in western countries (15-20).

All these studies demonstrated that screening with spiral CT allowed the detection of a high proportion of early-stage lung cancer cases. Furthermore, the International Early Lung Cancer Action Project reported a 10-year survival rate of 92% in patients with resectable stage I disease, whereas that of the whole study cohort was 80% (21). However, it was not a randomized controlled trial (RCT), and thus inevitably affected by cofounders. Therefore, we decided to focus our search on RCTs, in which the benefit of screening in terms of mortality reduction was directly compared between the study and control groups. The following 11 RCTs were found and their data were reviewed.

(I) LSS: Lung Screening Study (22-24);
(II) NLST (7,25);
(III) DANTE: Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Assays (26,27);
(IV) DLCST: Danish Lung Cancer Screening Trial (28,29);
(V) MILD: Multicentric Italian Lung Detection study (30);
(VI) NELSON: Nederlands-Leuvens Longkanker Screenings Onderzoek trial, or Dutch-Belgian Lung Cancer Screening Trial (31,32);
(VII) ITALUNG: Italian Lung Cancer Computed Tomography Screening Trial (33,34);
(VIII) Depiscan: a French pilot lung screening RCT (35);
(IX) LUSI: German lung cancer screening intervention study (36);
(X) UKLS: United Kingdom Lung Screening Trial (37);
(XI) JECS: Japanese randomized trial for evaluating the Efficacy of low-dose thoracic CT screening for lung cancer in non-smokers and smokers of 30 pack-years aged 50-64 years (38).

The NLST (7,25) was the largest study, comparing LDCT with CXR for lung cancer screening. The results indicated a reduction of 20% [95% confidence interval (CI), 6.8-26.7; P=0.004] in lung cancer-specific mortality and reduction of 6.7% (95% CI, 1.2-13.6; P=0.02) in all-cause mortality. The chance of dying from lung cancer was 0.33% lower for the LDCT group over the study period, and that is 1 lung cancer-specific death was prevented for every 310 individuals being screened. The other 10 smaller RCTs on

lung cancer screening using LDCT were conducted or are ongoing in the United States, Europe and Japan. To date, results from four studies, LSS, DANTE, DLCST, and MILD, have been reported. DANTE, DLCST, and MILD were conducted in Europe, whereas LSS was a pilot study of the subsequent NLST. Therefore, we only summarized results from NLST, DANTE, DLCST, and MILD in *Table 1*. However, all three European trials reported no mortality reduction benefit from LDCT lung cancer screening. The reasons for the inconsistent results have been previously discussed in several reviews (39,40). As shown in *Table 1*, a wide variability in the controls, sample size, demographic characteristics (sex and age), smoking history, tomogram thickness, screening intervals and duration, and follow-up duration might account for the different outcomes.

In addition, most screening studies were conducted in academic institutes or large hospitals with the participation of specialized thoracic radiologists and certified thoracic surgeons, which raises concerns about the effectiveness of screening in the community or at smaller facilities. Therefore, although LDCT screening appears promising, it is also a means of clinical intervention in its infancy with many unanswered questions, including the optimal time for screening initiation, duration, and intervals. Furthermore, other issues such as overdiagnosis, risk definition, patient selection, and financial burden also need to be carefully addressed. Although ongoing randomized trials might help resolve some of these matters and validate the NLST results, future studies are warranted to provide a definitive answer regarding the impact of LDCT screening on lung cancer-specific mortality at the population level.

Is it rational to offer LDCT screening for lung cancer to low-risk individuals?

The NLST reported that three annual rounds of LDCT screening resulted in a 20% relative decrease in death from lung cancer among high-risk participants, as compared to CXR. Further stratification of the participants into five risk categories using a validated prediction model showed that those with the lowest risk (the first quintile) accounted for only 1% of the prevented lung cancer-specific deaths, whereas 88% of the death prevention was from participants with a higher risk (the third to fifth quintiles) (41). Such a result indicated that individuals with a lower risk might benefit less from LDCT screening. Furthermore, the following potential limitations and harms associated with LDCT screening needed to be recognized:

(I) False-positive results: the average nodular detection rate was 20% in the NLST, but varied from 3% (42) to 30% (ITALUNG) in RCTs and 5% (16,43-45) to 51% (20,46) in cohort studies. In the NLST, 96.4% of the positive results in the low-dose CT group were false positive results across the three rounds and other studies reported that more than 90% of the nodules were benign (7,10,22,23,28,29,31-35);

(II) Radiation exposure: the effective dose of radiation from LDCT is estimated to be 1.5 mSv per examination, but it may vary in clinical practice. Furthermore, nodule detection might require more imaging procedures, such as diagnostic chest CT (about 8 mSv) (47) or positron emission tomography-CT (about 14 mSv) (47-49), which increases the total exposure and accounts for most radiation doses in these screening studies;

(III) Additional invasive procedures: in the NLST, 73% of patients with benign lesions had invasive nonsurgical procedures (7); 1.2% underwent invasive procedure such as needle biopsy or bronchoscopy, and 0.7% underwent thoracoscopy or mediastinoscopy (7). The percentage of unnecessary surgeries was 13% in DANTE and around 2% in other studies (50);

(IV) Death and complications: the frequency of death occurring within 2 months of a diagnostic evaluation of a detected finding was 8 per 10,000 individuals screened using LDCT and 5 per 10,000 of those who received chest radiography in the NLST. The majority of complications occurred after surgical procedures. In the total studied population, the risks of death and major complications following diagnostic events for benign nodules was higher in the LDCT group than in the chest radiography group (4.1 and 4.5 per 10,000 *vs.* 1.1 and 1.5 per 10,000, respectively) (50).

(V) Overdiagnosis: overdiagnosis is the detection of an extra quota of indolent tumors that would have no impact on patients' life expectancy even if undiagnosed. Although early RCTs of CXR suggested that lung cancer screening resulted in an overdiagnosis rate of exceeding 25% (51,52), it is impossible to estimate the definitive magnitude of overdiagnosis from the NLST because of the study design comparing LDCT and CXR. More evidence from prospective RCTs may eventually

Table 1 Summary of previously published randomized clinical trials on low-dose computed tomography screening for lung cancer

Trial name	Group (LDCT *vs.* control)	Recruitment years	N (LDCT *vs.* control)	Sex (F/M)	Eligibility criteria	Tomogram thickness (mm)	Screening intervals	Screening duration	Follow-up	Outcomes	Citations
NLST	LDCT *vs.* CXR	2002-2004	26,722 *vs.* 26,732	41/59	Age: 55-74 y; current or former (<15 years since quitting) smokers (≥30 pack-years)	1-2.5	0, 1, 2	3 y	6.5 y	Lung cancer specific mortality: reduction of 20.0% (95% CI, 6.8-26.7; P=0.004); all-cause mortality: reduction of 6.7% (95% CI, 1.2-13.6; P=0.02)	(7,25)
DANTE	LDCT *vs.* no screening	2001-2006	1,276 *vs.* 1,196	0/100	Age: 60-74 y; current or former smokers (≥20 pack-years)	5	0, 1, 2, 3, 4	5 y	2.8 y	LDCT *vs.* control number (%); lung cancer specific mortality: 20 (1.6) *vs.* 20 (1.7); all-cause mortality: 46 (3.6) *vs.* 45 (3.8)	(26,27)
DLCST	LDCT *vs.* no screening	2004-2006	2,052 *vs.* 2,052	44/56	Age: 50-70 y; current or former smokers (≥20 pack-years)	3 or 1	0, 1, 2, 3, 4	5 y	4.8 y	LDCT *vs.* control number (%); lung cancer specific mortality: 15 (0.7) *vs.* 11 (0.5); all-cause mortality: 61 (3.0) *vs.* 42 (2.1)	(28,29)
MILD	LDCT (annual or biennial) *vs.* observation	2005-2011	2,376 (1,190 annual, 1,186 biennial) *vs.* 1,723	34/66	Age: ≥49 y; current or former (quit <10 years ago) smokers (≥20 pack-years)	1-5	0, 1, 2, 3, 4	5 y	4.4 y	LDCT *vs.* control lung cancer specific mortality: HR =1.64 (95% CI, 0.67-4.01; P=0.21); all-cause mortality: HR =1.40 (95% CI, 0.82-2.38; P=0.13).	(30)

LDCT, low-dose computed tomography; F, female; M, male; y, years; CI, confidence interval; HR, hazard ratio; NLST, National Lung Screening Trial; DANTE, Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST, Danish Lung Cancer Screening Trial; MILD, Multicentric Italian Lung Detection.

provide an estimate of overdiagnosis rate;

(VI) Stage detection shifting: there is considerable interest in shifting detection to stages during which intervention could be curative. Screening did not reduce lung cancer stages detected after the first round, and only a slight decrease was reported in stage III and IV diseases detected in the third round compared with those found after the first round (37.8% *vs.* 30.4%) (7);

(VII) Psychological effect: false-positive findings and overdiagnosed tumors can cause anxiety. The NELSON trial results suggested that short-term lung cancer-specific distress was significantly high, but long-term evaluation indicated the resolution of such short-term anxiety; however, a second indeterminate finding was not associated with increased lung cancer-specific distress (53,54).

In addition to the above-mentioned limitations, there are other uncertainties regarding the harms and benefits of LDCT screening. An analysis of the NLST data using predicating models indicated that approximately 1 cancer death might be caused by radiation from imaging per 2,500 individuals screened (10), and the lung cancer-specific death prevention benefit was greater than the radiation risk that might manifest 10 to 20 years later. However, it would be less favorable for younger individuals or those with a low risk of developing lung cancer (10). Therefore, the NLST findings should be neither minimized nor overstated when more data on LDCT screening are due to be reported in the near future. Additionally, considerable risks must be overcome before LDCT can be widely offered as a preventative screening method to those at risk of developing lung cancer. Currently, LDCT may not be cost-effective when provided to individuals with a low risk of lung cancer development, especially in a setting that might involve higher frequency of unnecessary interventions and procedures. Thus, for optimal cost-effectiveness, individuals with a sufficiently high risk of developing lung cancer need to be identified so that the benefit-to-harm ratio of the screening can be maximized (55).

Is there a clear definition of high and low risk for lung cancer development?

As shown in the NLST, screening using LDCT prevented the greatest number of deaths among participants who were at the highest risk for the disease, whereas the number of prevented death was very limited for those at the lowest risk. These findings provided the empirical support for risk-based targeting for such screening. Although it is generally agreed that screening should be limited to high-risk individuals for whom the potential benefits of LDCT screening would outweigh its harms, the exact definition of such a high-risk population is unclear.

Most available recommendations are based on the NLST high-risk criteria, which focus only on patients' age and smoking history. Although such a definition of risk was practical for the purpose of a clinical trial, it is not as useful for screening target selection because certain valuable predictors are omitted. Smoking accounts for 80% of the worldwide lung cancer burden in men and at least 50% of that in women (56); however, approximately 85% of heavy smokers do not develop lung cancer (57). Moreover, the NLST enrolled a younger and healthier population with only 8.8% of the study participants in the oldest category (70-74 years) (7), which might challenge the generalization of the study results to that age group. This particular point cannot be overstated, as the average age of lung cancer diagnosis is 70 years, and it should make clinicians wary of applying the mortality statistics for surgery to individuals in the oldest group.

In addition, other risk factors associated with lung cancer includes second-hand smoking (58); exposure to solid fuel smoke (59) or outdoor particulate matter (60); occupational exposures (61); family history (62); genetic polymorphisms such as those in tumor protein p53, excision repair cross-complementation group 1, or methylenetetrahydrofolate reductase (63-65); radon (66); other pulmonary diseases (67); and sex differences (68). Furthermore, it would be politically problematic to offer publicly funded medical interventions solely to heavy smokers, when non-/light smokers might also be at a high risk owing to other environmental, occupational, and genetic factors. Meanwhile, the low detection rate for prevalent and especially incident lung cancers are key elements in explaining the high cost-effectiveness ratio of lung cancer screening using LDCT alone. This clearly indicates the need for multidimensional integrated strategies to increase the rate of screen-detected lung cancers with LDCT, possibly via the inclusion of subjects with other risk factors besides smoking history and age.

Multiple lung cancer risk prediction models with good performance have been established to facilitate such strategies. An accurate risk prediction model is more efficient in identifying individuals who are likely to develop lung cancer and die from the disease than simple factors such as age and pack-years of smoking. Currently,

there have been many lung cancer risk prediction models developed. Different models have included variable risk factors which could be categorized into epidemiology factors, clinical factors as well as genetic and molecular biomarkers. We picked out the most popularly studied models, and list the risk factors incorporated in each model (shown in *Table 2*).

Although the validation of these models shows moderate to high discrimination and calibration, there are certain limitations that can affect their accuracy and application. First, Maisonneuve *et al*. found that the common epidemiological risk factors had relatively low discriminatory power to predict the possibility of lung cancer development; therefore, clinical factors as well as genetic and molecular biomarkers were used to develop models, but their validation was insufficient (73). Second, the study participants selected to validate these models might not be adequately representative for generalization. For example, the participants in the Tammemagi model were 55-74 years of age at the time of enrollment and in general, were of higher socioeconomic status than the general population, possibly resulting in a healthy volunteer effect and limiting the model's external generalizability (69). Third, categorization of continuous data could lead to loss of information and predictive ability, as used in the Bach and Liverpool Lung Project models which divided continuous smoking history data into four categories (71,75). Fourth, selection of predictive variables for entry into the multivariable models was based on a P value of less than 0.05 in univariate analysis, which could result in important predictors being left out more often than when a less stringent P value cut-off was used, such as in the Spitz model (78).

Currently, no prediction model is utilized in clinical settings. Among the clinical trials on lung cancer screening, only the UKLS applied a prediction model for selection criteria. The better understanding of lung cancer and identification of more potential risk factors could make screening for the disease more accurate and complex at the same time, and the current prediction models could certainly be improved. Therefore, it is difficult to provide an accurate definition of high or low risk for lung cancer. Only the screening guidelines issued by the NCCN in 2011 defined low-risk individuals as those aged <50 years and/or having a smoking history of <20 pack-years, and lung cancer screening was not recommended for these (6). The incorporation of other well-known risk factors has not been studied. Thus, there is currently no evidence to suggest a re-assessment of screening selection criteria. In order to identify individuals for whom the harm/benefit balance of LDCT screening is favorable, a good risk prediction model for lung cancer is certainly needed.

How should we address the current and future implementation of LDCT screening?

The international debate on whether to implement CT lung cancer screening programs is ongoing with unresolved issues. To date, screening programs have reported that 6%~34% of all patients with benign lesions have undergone surgical treatment. Such variability is due primarily to the different protocols used and providers' experience. Therefore, only the adoption of a shared protocol and experienced multidisciplinary teams may ensure the lowest possible rate of futile procedures.

An international review of lung cancer screening was conducted during a workshop convened by the International Association for the Study of Lung Cancer, and its report was published (84) after that of the NLST results. The workshop participants provided six recommendations for future priorities: to identify high-risk individuals for lung cancer CT screening programs, to develop radiological guidelines for use in developing national screening programs, to create guidelines for the clinical work-up of indeterminate nodules resulting from CT screening programs, to develop guidelines for pathology reporting of nodules from lung cancer CT screening programs, to make recommendations for surgical and therapeutic interventions of suspicious nodules identified through lung cancer CT screening programs, and to integrate smoking cessation practices into future national lung cancer CT screening programs. However, optimum resolutions of the issues are still awaited.

The ongoing RCTs are likely to provide further evidence for mortality reduction advantage of CT screening and its cost-effectiveness. They might also offer a better insight into risk stratification of the general population who need to be screened and a robust radiological protocol to reduce false-positive results and help with management decisions about indeterminate nodules. Additionally, in-depth data are now emerging from the use of minimally surgical approaches, especially video-assisted thoracoscopic surgery for small CT-identified nodules. All these factors will contribute greatly to reducing the harms and increasing the benefits of CT screening. In the meantime, we need to prepare for lung cancer screening with an integrated smoking cessation policy because this combined

Table 2 Risk factors incorporated in the risk models for lung cancer

Models	Risk factors						Citations
	Epidemiology factors				Clinical factors	Genetic and molecular biomarkers	
	Socio-demographic factors	Medical history	Environmental/ occupational exposures	Smoking history			
Tammemagi model	Age, BMI, education, race, sex	COPD, chest radiography in past 3 years, family history of lung cancer		Duration, quit time, smoking status, smoking, intensity, pack-years, smoked			(69,70)
Bach model	Age, education, race, sex,		Asbestos	Duration, quit time, smoking status, smoking, intensity			(71-74)
LLP model	Age, sex	Pneumonia, family history of lung cancer, prior diagnosis of malignant tumor	Asbestos	Duration			(75)
Etzel model	Sex	Hay fever, COPD	Asbestos, dust, environmental tobacco smoke	Duration, smoking status, smoking intensity, pack-years smoked			(76)
Park model	Age, BMI, physical activity	Family history of cancer, fasting glucose level		Smoking status, smoking intensity, age at smoking initiation			(77)
Spitz model	Age	Emphysema, hay fever, family history of cancer	Asbestos, dust	Smoking status, pack-years smoked, years of cessation, age at smoking initiation, age at smoking cessation			(78)
EPIC model	Age, BMI, education, sex	Asthma, hay fever, family history of cancer	Polycyclic aromatic hydrocarbons, silica, metal, asbestos	Smoking status pack-years smoked, years of cessation, age at smoking initiation, age at smoking cessation		Chr 15q25, Chr 5p15	(79)
Hippisley-Cox model	Sex	COPD, prior cancer, Townsend deprivation score	Asbestos	Smoking status, smoking intensity	Current hemoptysis, current appetite loss, current weight-loss, cough in last year, hemoglobin <11 g/dL in the last year		(80)

Table 2 (*continued*)

Table 2 (*continued*)

Models	Risk factors						Citations
	Epidemiology factors				Clinical factors	Genetic and molecular biomarkers	
	Socio-demographic factors	Medical history	Environmental/ occupational exposures	Smoking history			
Iyen-Omofoman model	Age, sex	COPD, respiratory tract infection, Townsend score		Smoking status, smoking intensity	Hemoptysis, cough, chest/shoulder pain, dyspnea, weight loss, voice hoarseness, chest infections, No. of general practitioner consultations		(81)
Expanded Spitz model		Emphysema, hay fever, family cancer history	Dusts, asbestos	Smoking status, pack-years smoked, age stopped smoking		DNA repair capacity, bleomycin sensitivity	(82)
Improved LLP model		Pneumonia, previous tumor, family history of cancer, goodness-of-fit statistic	Asbestos	Duration		SEZ6L genotype marker	(83)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; LLP, Liverpool Lung Project; EPIC, European Prospective Investigation into Cancer and Nutrition.

approach might save more lives than any other lung cancer intervention in the near future.

Conclusions

The high incidence and mortality of lung cancer highlights the need for ongoing prevention and control strategy to reduce the disease burden. Although LDCT showed promising results in the NLST trial and has become a recommendation for lung cancer screening in many guidelines, there are still debates on its cost-effectiveness. The value of LDCT in lung cancer screening for high-risk individuals should be confirmed in more trials. Currently, the procedure is not recommended for low-risk patients, although some might be missed based on the current definition of risk factors. The accurate definition of risk factors and better predictive models are particularly important for future lung cancer screening trials. Further studies are urgently needed to solve the problems involved in lung cancer screening in order to improve the disease's outcomes.

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Footnote

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Implementation of lung cancer screening: promises and hurdles

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Abstract: Lung cancer screening is a subject of considerable interest in the medical community and the general population. Since the publication of the data from the national lung screening trial (NLST) in 2011, the interest in lung cancer screening has increased even more. Data from many sources provide evidence that low-dose computed tomography (LD-CT) lung cancer screening can be performed with even greater efficacy if inclusion criteria as well as nodule management are optimized. There are, however, also a number of potential hurdles for the implementation of lung cancer screening. Among these are, in particular, the high prevalence of screen-detected pulmonary nodules, the unknown extent of over-diagnosis, the potential harms of the cumulative radiation dose and the insufficient data on cost-efficiency of lung cancer screening. In this article, the most recent insights into some of the most imminent questions are reviewed to provide an understanding of the challenges we still face in lung cancer screening.

Keywords: Lung cancer screening; pulmonary nodules; lung cancer

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Introduction

Lung cancer screening has gained considerable interest in the medical community, as well as in the general population, over the last two decades. Since the publication of the data from the national lung screening trial (NLST) in 2011, the interest in lung cancer screening has increased even more. With more than 50,000 enrolled persons, the NLST could prove, for the first time, that by using lung cancer screening with low-dose computed tomography (LD-CT)—compared to screening with chest radiographs—lung cancer mortality could be improved by 20% (1). In addition to lung cancer mortality, overall mortality could also be improved in the LD-CT screening group by 6.7% (1). The promising data from the NLST encouraged several major American medical societies to recommend offering LD-CT screening for high-risk patients (2-4). In a current survey among members of the Society of Thoracic Radiology, 65.9% of the responding institutions indicated that they had an active LDCT screening program (5). Of the institutions without an active screening program, 89.3% indicated that they were considering such a program in the future (5). The results of this survey indicate that lung cancer screening has finally arrived in many centers in the US.

While LD-CT lung cancer screening is implemented in more and more US centers, there are only a few LD-CT screening projects in Europe outside screening trials. The reservation about the implementation of screening projects in Europe can, in part, be explained by the ongoing screening in many countries where results are expected to be published within the next few years. Initial data from two Italian screening trials (the MILD trial and the DANTE trial) and one Danish trial (the DLCST trial) could not confirm the positive effect of LD-CT lung cancer screening on mortality (6-8). The number of participants in all of the three trials, however, is too small to reach statistical significance.

Although the majority of the ongoing European screening trials are statistically underpowered, a pooling of the data is expected to strengthen the evidence and to provide insights into many open questions.

Promising data from the NLST and other trials provide evidence that LD-CT lung cancer screening can be performed with even greater efficacy if inclusion criteria,

as well as nodule management, are optimized. There are, however, also a number of potential hurdles for the implementation of lung cancer screening. Among these are, in particular, the high prevalence of screen-detected pulmonary nodules, the unknown extent of over-diagnosis, the potential harms of the cumulative radiation dose and the insufficient data on cost-efficiency of lung cancer screening. A broad implementation of LD-CT screening largely depends on answering most, if not all, of these questions. In this article, the most recent insights into some of the most imminent questions are reviewed to provide an understanding of the challenges we still face in lung cancer screening.

Who should be screened?

The positive effect of lung cancer screening depends, to a great degree, on the prevalence of lung cancer in the screening population. In the NLST, only persons between 55 and 74 years of age and a smoking history of more than 30 years, or former smokers who quit smoking within the previous 15 years, were included (9). These inclusion criteria defined a study population with an estimated risk of developing lung cancer, ranging from 2% to more than 20%, within 10 years (10). The positive effect of lung cancer screening could be increased even further by adding additional inclusion criteria, such as gender, passive smoking history, history of pneumonia, history of non-pulmonary tumors, or occupational exposure to asbestos.

Using the data from the NLST, a risk prediction model for lung cancer death was recently published, which used the risk factors of age, body-mass index, family history of lung cancer, pack-years of smoking, years since smoking cessation, and emphysema diagnosis to estimate the 5-year risk of lung-cancer death (11). This retrospective study confirmed that the number of prevented lung-cancer deaths increased with increasing risk quintiles (11). In the quintile with the lowest risk, only very few deaths (1%) would have been prevented. In fact, 88% of the prevented lung-cancer deaths were distributed among the three quintiles with the highest risk (11).

The impact of a more sophisticated risk model on the effectiveness of lung cancer screening is currently being investigated in the ongoing British UK lung screen (UKLS) trial. In this trial, only patients with an at least 5% risk for developing lung cancer within the next five years are included. The risk for developing lung cancer is estimated using a model developed in the Liverpool Lung Project (LLP) (12). The LLP risk prediction model includes age, sex, smoking duration, family history of lung cancer, history of non-pulmonary malignant tumor, history of pneumonia, and occupational exposure to asbestos to estimate the lung cancer risk (12). It is projected that, by using these inclusion criteria, the prevalence of lung cancer in the screening population will be twice as high as in the Dutch NELSON trial (13).

At what intervals should the screening be planned?

The screening interval has a direct impact on screening performance, as well as overall costs and the cumulative radiation dose. Long screening intervals carry the risk that, aggressively growing tumors, in which the interval between the origin of the tumor, its detectability by CT, and the point at which it manifests, is quite rapid, may not be detected in early stages. Thus, screening would detect mainly indolent, slowly growing tumors. However, short screening intervals increase the probability of detecting aggressive cancers with the shortcoming of increasing the overall costs and cumulative radiation dose.

To date, most of the prospective screening trials were designed with annual screenings for three or five years (1,6,8,14). However, although not yet investigated in a prospective trial, biennial (twice-yearly) screening could have the potential to be more cost-effective than annual screening. A current prediction model based on the UK lung cancer screening eligibility criteria and the NLST data suggests that the intervention effect of biennial screening could indeed justify the human costs (15). Prospective trials will be necessary to further investigate the effect of biennial screening on survival.

How should detected nodules be managed?

One of the major challenges of lung cancer screening is the high incidence of detection, coupled with a very low proportion of malignant nodules. In the NLST, a positive screening result was reported in 24% of all baseline LD-CT scans (1). A positive screening result was thereby defined as a non-calcified pulmonary nodule with a maximum diameter of more than 4 mm. Importantly, all but 3.6% of the detected pulmonary nodules eventually proved to be benign in nature (1). Most of the detected nodules were further evaluated with follow-up CT examinations, and only 2.6% of the nodules were surgically resected. Even though the majority of the nodules were investigated with

follow-up examinations or minimally invasively, the added cost and cumulative radiation dose, the potential risks of these examinations, and, last but not least, the anxiety of the screened persons with a positive result are of major concern. As the probability of malignancy increases with increasing nodule diameter, using a threshold for nodule diameter, which would define positivity to 7 mm, would decrease the early recall rate by up to 70% (16). By considering additional data besides the size of the nodules, such as the location of the nodule, the number of detected nodules, the sex and age of the screened person, and the extent of emphysema, the risk of malignancy of the nodules could be even better predicted and the recall rate could be reduced even further (17).

Much has been done in the last few years to provide a reliable classification scheme for screening-detected nodules. Analogously to the Breast Imaging Reporting and Data System (BI-RADS) of the American College of Radiology (ACR), which is used worldwide in breast cancer screening, the ACR recently proposed a Lung Imaging Reporting and Data System (Lung-RADS) (18). A similar system, the Lung Reporting and Data System (LU-RADS), was published by another group (19). In both classification schemes, screening-detected nodules are categorized and managed according to their individual risk. Both classification schemes should be easy to apply in the clinical routine and allow standardized data collection and analysis.

How big is the risk of over-diagnosis?

One of the major uncertainties in lung cancer screening is the extent of over-diagnosis. Over-diagnosis is defined as the detection of cancer that otherwise would not become clinically apparent (20). Thus, the detection of lung cancer during screening does not necessarily result in improved lung cancer mortality, as a proportion of the detected cancers would have remained asymptomatic. Follow-up and treatment of such indolent cancers would add to the costs and potential risks of screening. Early reports concluded that the proportion of over-diagnosed cases could be as low as 5% (21). More recent data, however, indicate that the extent of over-diagnosis in the NLST could have been more than 18% (20). This estimation is almost as high as in a study based on data from an Italian cohort study, which estimated that over-diagnosis could be as high as 25% (22).

To date, there are no generally accepted criteria by which to differentiate indolent tumors from genuine ones. Strategies to reduce over-diagnosis focus on a reduction of the frequency of screening examinations, a better definition the screening population, and raising the threshold for follow-up examinations and invasive diagnosis (23).

How cost efficient is lung cancer screening?

Little is known about the cost-efficacy of lung cancer screening, which was considered to be a major hurdle for the implementation of a screening project. An actuarial analysis demonstrated, however, that, in the United States, lung cancer screening in high-risk populations would cost insurers less per life-year saved than colorectal, breast, or cervical cancer screening (24). Similar data comes from a study from Israel which showed that baseline LD-CT screening can be performed with relatively low costs per quality-adjusted life-year (QALY) (25). In this study, the estimated cost per QALY gained was as low as $20,000 (25). As health care systems differ significantly between countries, cost-efficacy analyses from one country cannot easily be translated to other countries.

What is the potential risk of the cumulative radiation dose?

The discussion about the potential risk of the cumulative radiation dose in LD-CT lung cancer screening from repeated screening CTs and potential follow-up CTs, has evened out in the last few years. In the NLST, the reported effective dose per screening CT was an average of 1.6 mSv for men and 2.1 mSv for women (25). However, due to the high number of follow-up examinations, the average cumulative radiation dose after three screening rounds added up to 8 mSv (10). This cumulative radiation dose was estimated to cause one cancer death per 2,500 persons screened (10). However, as in the NLST, lung cancer screening was able to improve the overall mortality by 7%; thus, the positive effect of screening outweighs the risk of radiation-induced cancer.

As modern CT scanners are able to scan the whole chest with less than 1 mSv, and future staging protocols will be performed with a dramatically lower recall rate, the cumulative radiation dose will decrease, and thus, the risk-benefit ratio will further improve.

Conclusions

More data from many different sources provide evidence that LD-CT lung cancer screening can be performed with

a higher efficacy if inclusion criteria, as well as nodule management, are optimized. However, to date, only NLST has been able to show the benefits of LD-CT screening with regard to lung cancer and overall mortality. The promising data of the NLST is further supported by analyses, which have demonstrated, that LD-CT lung cancer screening can be performed with even greater efficacy if inclusion criteria as well as nodule management are optimized.

In addition, more and more data provide evidence to overcome potential hurdles in lung cancer screening such as questions regarding the extent of over-diagnosis and potential harms of the cumulative radiation dose. Questions regarding cost-efficiency of lung cancer screening have to be answered for each healthcare system separately.

As most of the data derives from one single study, the NLST, the data, needs to be confirmed, at least in part, by the pooled data of the ongoing European trials.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Potential biomarkers for lung cancer screening

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Abstract: Notwithstanding the encouraging results of the National Lung Screening Trial (NLST) the scientific community still debates on the cost-benefit profile of low dose computed tomography (LDCT) lung cancer screening. Several major concerns regard how to identify subjects at high risk of developing lung cancer, the optimal diagnostic algorithm, the management of lung nodules and the high false positive rates. The use of complementary biomarkers would be a useful strategy for dealing with most of these issues. This short review will focus on candidates' biomarkers circulating in serum or plasma that already reached an advanced validation phase also in LDCT lung cancer screening series. The biomarkers presented below are examples of the value of searching candidates by looking not only to the tumor itself but also to the interplay between the tumor and the host in order to identify early changes related to the biological reactivity of the host to a developing cancer.

Keywords: Lung cancer; risk prediction; screening; diagnosis; prognosis; biomarkers

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Background

Lung cancer is the second most frequent cancer both in man and women and continues to be the leading cause of death from cancer, accounting for over 20% of all cancer deaths in 2012 in Europe (http://globocan.iarc.fr).

The overall 5 years survival rate for lung cancer has risen from only 12% to 16% in the past 4 decades, due largely to the late stage at which most patients are diagnosed. This rate is very small if compared to that observed for the other big killers, colon and breast cancer, where survival exceeds 70% and 50%, respectively. In contrast survival of patients undergoing lung resection for small intrapulmonary cancers is greater than 80%. Thus in lung cancer, more than in any other cancer, early detection is essential to improve survivability through identification and therefore treatment of patients before their cancers become inoperable and lethal.

Imaging modalities and biomarkers

Great enthusiasm was raised by the publication in 2011 of the results of the National Lung Screening Trial (NLST), a randomized clinical screening trial enrolling 53,454 persons with three rounds of low dose computed tomography (LDCT) annual screening versus chest radiographs (1). It demonstrated a 20% reduction of lung cancer mortality and 7% reduction of all cause mortality in favor of LDCT. However, after three rounds of screening, 24.2% of subjects were classified as positive with 96.4% of these being a false positive with the need to screen 320 subjects to prevent 1 lung cancer death.

In a recent paper from the same team the issue of overdiagnosis in the trial was estimated (2). The authors reported an overdiagnosis global rate of >18% and that the number of cases of overdiagnosis in the 320 subjects needed to be screened to prevent 1 lung cancer death is 1.38. Thus reduction of false positive rate after initial screen, as well as reduction of overdiagnosis by more efficient prediction of tumor aggressiveness, represents critical and still unmet clinical needs.

Recently the results of three smaller European LDCT

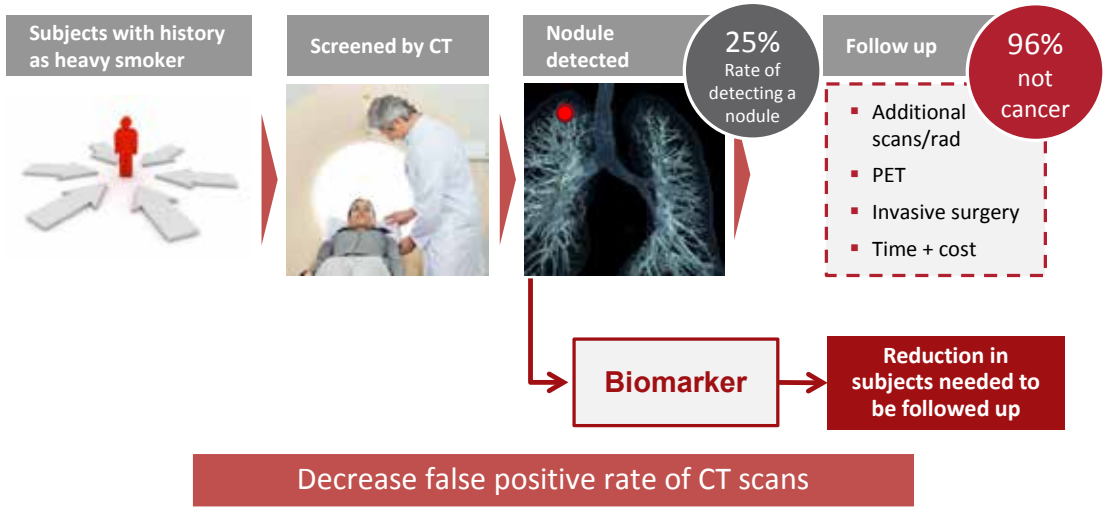

Figure 1 Clinical utility of biomarkers.

screening randomized trials were published and have reported non-significant mortality reductions (3-5). Two studies, the Multicentric Italian Lung Detection (MILD) (3) and the Danish Lung Cancer Screening Trial (DLCST) (5) showed a higher mortality in the screened LDCT arm and a meta-analysis of the four published studies demonstrated a small benefit in lung cancer mortality reduction (3).

In a systematic review of all randomized clinical trials that examined the benefits and harms of LDCT screening, the average nodule detection rate was around 25%, with 96% of nodules being benign. These high false positive rates of LDCT lead to multiple screening rounds and related radiation exposure, the use of unnecessary and sometimes harmful diagnostic follow-up and increased time and costs. The development of non-invasive complementary biomarkers could thus be very helpful for the reduction of subjects needed to be followed up and potentially to decrease false positive rate of CT scans and the over-diagnosis rate (*Figure 1*).

Biomarkers circulating in plasma or serum, if properly validated, could constitute the gold standard for a non invasive cancer diagnostics. In fact blood thanks to its rich content of different cellular and molecular elements that provide information on the health status of an individual, constitutes the ideal compartment to be tested for developing biomarkers. Moreover, blood samples can be easily and inexpensively collected by non invasive procedures throughout large clinical trials.

Several authors have based their biomarkers discovery strategy starting from the assumption that novel promising biomarkers are generated not only by cancer cells but also from the tumor microenvironment, the host response and their dynamic interaction. The cross talk among these components can be reflected in peripheral circulation and generate diagnostic and prognostic biomarkers and potentially, also biomarkers predicting the risk of disease development.

Table 1 reports the most promising candidate biomarkers for early lung cancer diagnostics detected in blood and their respective development phases according to the guidelines published in JNCI (6) and taking also into account the workflow for biomarkers validation described by other authors (7,8).

Several biomarkers have reached phase 3 which evaluates, as a function of time before clinical diagnosis, the capacity of the biomarker to detect preclinical disease. However, only few of them reached phase 4, prospective screening, which studies screen people and lead to diagnosis and treatment. None of them has reached so far phase 5, the final phase that will address whether screening with selected biomarkers will result in an overall benefit for the screened population by impacting on survival. A good biomarker should reduce the burden of cancer and would be not useful if it does not lead to change in treatments or outcomes and if it is only efficient in picking up indolent cancers.

However, concerning biomarkers, it must be recognized that there is a disconnection between promise and product and several reasons could be evoked:

- Discovery methods are often neither reliable nor efficient. This is in part related to the rapidly changing technology;

Table 1 Circulating biomarkers for early lung cancer

	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Candidates	Discovery, prediction	Assay validation	Retro-longitudinal	Prospective screening	Cancer Control
Autoantibodies (earlyCDT-test)	×	×	×	×	
C4d protein	×	×	×		
Serum microRNA	×	×		×	
Plasma microRNA (MSC test)	×	×	×	×	

- Selection of candidates: the choice of tumor-specific or high-throughput approaches. In particular genetic heterogeneity of tumors has limited the success of these initiatives;
- Reproducibility of the laboratory assays: several studies have to deal with over fitting, and lack of cross-validation and external validation;
- Most studies have poor design, just rely on case-control comparison and are not in the clinical context;
- The low concentration of analytes to be measured influences the reproducibility of the results;
- The availability of very few prospective collections of biological samples and in particular of bio-repositories related to screening trials.

Blood-based biomarkers

This review will focus on candidates' biomarkers circulating in serum or plasma since they are so far those that reached the more advanced validation phase.

All the studies selected in this review have validated their biomarkers in the context of LDCT lung cancer screening trials, by studying high risk subjects, and showed to be of value to predict the risk of lung cancer in asymptomatic individuals.

The biomarkers presented below are also examples of the value of searching candidates by looking not only to the tumor but also to the interplay between the tumor and the host in order to identify early changes related to the biological reactivity of the host to an incipient cancer.

Immune response biomarkers

C4d complement split product (9)—Phase of development: phase 2

These authors used an alternative approach not looking for cancer but for the immune response to cancer. In fact, immune activation may generate host-derived markers that are more homogeneous than cancer-derived markers. Immune responses against intracellular and surface tumor antigens are well documented in patients with lung cancer (10). In particular, the complement system is activated in lung tumor cells (11-14). Complement is a central component of innate immunity that plays an essential role in immune surveillance and homeostasis (15).

In their study these authors showed that lung tumors activate the classical complement pathway and generate C4d, a degradation product of this pathway and they evaluated if C4d may be of value for the diagnosis and prognosis of lung cancer.

They first examined plasma samples from 50 patients with early (stage I-II), clinically detected lung cancer and showed statistically significantly higher levels of C4d than those from 50 matched control subjects. The area under the ROC curve was 0.782 ($P<0.001$). Patients with higher levels of C4d (>3 μg/mL) had a statistically significantly shorter overall survival than those with low C4d levels ($P=0.002$). They also measured the levels of C4d in paired plasma samples (pre- and post-surgery) from 25 lung cancer patients with high (>2 μg/mL) C4d levels in the pre-surgery plasma. In all but one case, C4d levels were reduced after surgical removal of the tumor ($P<0.001$). As expected, in 19 patients with low plasma C4d levels (<2 μg/mL), the concentration of the marker did not change after resection of the tumor. These results provided evidence that plasma C4d levels depend on the presence of the tumor.

Plasma C4d levels were further evaluated in plasma samples from 190 asymptomatic individuals enrolled in a LDCT screening program. Thirty-two of them were diagnosed with lung cancer in the context of the program while the remaining 158 individuals had no evidence of cancer after LDCT screening. Both groups were matched

Table 2 Performances of the autoantibody EarlyCDT®-Lung test

	Cases	Controls	Sensitivity	Specificity
Case-control studies	235	266	41%	91%
Clinical audit dataset	61	1,538	41%	87%
CT-detected lung nodules	43	146	44%	88%

by sex, age, and smoking history. Plasma C4d levels were statistically significantly higher in individuals with lung cancer than in individuals without the disease.

This result suggests that C4d levels may be of value to predict the risk of lung cancer in asymptomatic individuals. Additional validation sets are required to establish reliable cutoff values of this biomarker and it would be also critical to evaluate the performance of the test in specific clinical applications (e.g., in the context of a screening program) or in a cohort of prospectively collected patients presenting with one or more lung nodules discovered by chest LDCT.

Autoantibody signature (16)—Phase of development: phase 4

A more advanced and validated biomarker is the Autoantibody (AAB) signature developed by the group of Richardson JF in United Kingdom and now released by Oncimmune USA LLC.

It is well established that cancer patients produce autoantibodies to tumor proteins that are mutated, misfolded, ectopically presented, over-expressed, aberrantly degraded or anomalously glycosylated.

These authors discovered a 7 AAB signatures, previously 6 AAB, against oncogenes and TSG involved in lung cancer and also in other tumors: CAGE, GBU 4–5, HER2, p53, c-myc, NY-ES0-1 and MUC1. The strength of this AAB signature, called EarlyCDT-Lung test, is that it was validated in large series of patients and controls including either early and late stages tumors, NSCLC and SCLC. Across the various series, the signature showed high specificity, around 93%, but quite low sensitivity ranging around 40% in NSCLC and 55% in SCLC (*Table 2*) (16-20). However the test has the advantage to rely in an Elisa assay that is easily accomplished in a clinical laboratory.

In a recent paper (21) the test's performance characteristics in routine clinical practice were evaluated by auditing clinical outcomes of 1,600 US patients deemed at high risk for lung cancer by their physician, who ordered the EarlyCDT-Lung test for their patient.

The results obtained mirrored that of the extensive case–control training and validation studies previously reported (17-19,22). This audit has confirmed that EarlyCDT-Lung detects all types of lung cancer, all stages of the disease, and performs in clinical practice with the same sensitivity and specificity measured in the case–control studies. This is, therefore, the first autoantibody test that detects early stage lung cancer as shown with prospective validation data on a large number of individuals from a routine clinical practice setting (*Table 2*).

Recently Massion *et al*. evaluated the performance of the 7 AAB test in 189 lung nodules detected by LDCT, of which 43 malignant and 146 benign, and reported that EarlyCDT- Lung Oncimmune can provide significant discrimination between malignant and non-malignant lung nodules with sensitivity 44.2%, specificity 88.4%, PPV 52.8%, NPV 84.3%, with even better performance for nodules between 8-20 mm of diameter (*Table 2*) (unpublished data).

A prospective study is ongoing in Scotland (ECLS study) with the purpose to assess the value of the EarlyCDT-Lung test as a pre-CT screening tool. The study will enroll 10,000 people (50-75 yrs, smokers or ex-smokers) from Glasgow and the surrounding areas. Half of those taking part will be offered the EarlyCDT-Lung test (lung cancer test group). The other half (non-test group) will also have their blood taken, but it will not be tested as part of this study. People who have a positive lung cancer blood test will get a chest X-ray and a lung scan and 6 monthly scans for 2 years. However, only 1 in 9 people with a positive test is expected to develop LC within 2 years. People with a negative lung cancer blood test and those in the non-test group will not get any X-rays or scans will be monitored by their GP as normal: 98-99/100 people with a negative test are expected to not have LC at that time.

This study will potentially give insights on the utility of this biomarker as a first-line test to select subjects at increased risk for lung cancer development who need to undertake regular LDCT , potentially avoiding radiological exposure to low risk individuals with a negative test.

Blood circulating miRNAs

Circulating microRNA in plasma and serum are promising biomarkers for a non invasive cancer diagnostics. After being transcribed in the nucleus, pre-miRNA molecules can be processed further by Dicer in the cytoplasm. In addition, based on recent findings there are at least two ways that pre-miRNAs can be packaged and transported using exosomes and MVBs or other (not fully explored) pathways together with RNA-binding proteins. After fusion with the plasma membrane, MVBs release exosomes into the circulating compartments and bloodstream. Likewise, pre-miRNA inside the donor cell can be stably exported in conjunction with RNA-binding proteins, such as NPM1 and Ago2, or by HDL (23). Circulating miRNAs enter the bloodstream and are taken up by the recipient cells by endocytosis or, hypothetically, binding to receptors present at the recipient cellular membrane capable of recognizing RNA-binding proteins. More studies are necessary to elucidate how miRNAs are loaded into exosomes and how they can be internalized by recipient cells. Exosomal miRNAs are processed by the same machinery used in miRNA biogenesis and thus have widespread consequences within the cell by inhibiting the expression of target protein-coding genes.

Thus, for their nature and biogenesis, miRNAs seem to remain rather intact and stable in biological fluids and, importantly, they are detectable quantitatively with simple assays (i.e., RT-qPCR) that are suitable also in a clinical context.

Serum-based 34 miRNA signature (24)—Phase of development: phase 4

The group of F. Bianchi at European Institution of Oncology (Milan, Italy) has developed a blood test for lung cancer diagnosis in asymptomatic high-risk individuals (heavy smokers, aged over 50) based on the detection of miRNAs from serum. Sera were collected from high-risk subjects enrolled in a large prospective early detection trial (the COSMOS study) for lung cancer by annual LD-CT. Starting from a total of 365 miRNA assay (microfluidic cards) the authors selected a pool of 147 miRNAs that were informative in a total of serum 253 samples from lung cancer screening patients and controls (COSMOS), symptomatic lung cancer patients and as a control group, a breast cancer and benign nodules series (*Figure 2*).

They used the training set to derive a diagnostic 34-miRNA signature capable of separating tumor from normal sera. As discriminant predictor a risk index was calculated based on the inner sum of the weights (*wi*) and expression (*xi*) of the 34 miRNAs greater than the threshold determined in the training set ($S\ wi\ xi>3.235$).

The performance of the IEO test in the validation set was 71% sensitivity, 90% specificity and 80% accuracy with better performance in stage II-IV only (30 normal/12 tumors) with 82% sensitivity, 90% specificity and 90% accuracy.

An analysis of the 34-miRNA model prediction strength in the testing set (all, 30 normal and 34 tumors) stratified by available clinical-pathological parameters showed odds ratio higher in Stage II-IV disease, in squamous carcinoma and in women.

When the 34-miRNA predictor was applied to evaluate the risk in a symptomatic set of 36 NSCLC patients and in 15 pulmonary hamartomas, it performed remarkably well.

By comparing the performance of the predictor in the normal sera of the testing set and in the sera of patients with the LDCT-detected benign nodules no significant differences in the average risk of the normal and nodule categories were found.

The authors also analyzed a group of sera collected before the onset of NSCLC (i.e., from patients who were negative at the screening round but who developed lung cancer >1 year after). For 13 of such cases, both the sera harvested before disease onset (BDO) and the tumor sera that were already included in the training or testing sets were available. When the risk predictor algorithm was applied, it indicated a significantly increased average risk index for sera collected after the onset of the disease (average risk BDO, 7.1; tumor, 10.4; $P<0.001$, paired *t*-test). Thus, at least in the cases analyzed, the 34-miRNA model was capable of detecting the conversion from a normal to a malignant state.

Finally, they tackled the question of the specificity of the 34-miRNA predictor for NSCLC detection, as opposed to other types of cancer, by screening sera from a cohort of 18 patients with invasive ductal breast carcinoma and 10 with breast benign nodules. When the 34-miRNA risk predictor algorithm was applied, it could not discriminate between breast tumors and benign breast nodules.

Plasma-based miRNA signature (25)—Phase of development: phase 4

In our first exploratory study we investigated miRNA profiles in plasma samples collected before and at time of disease detection in subjects enrolled in the first

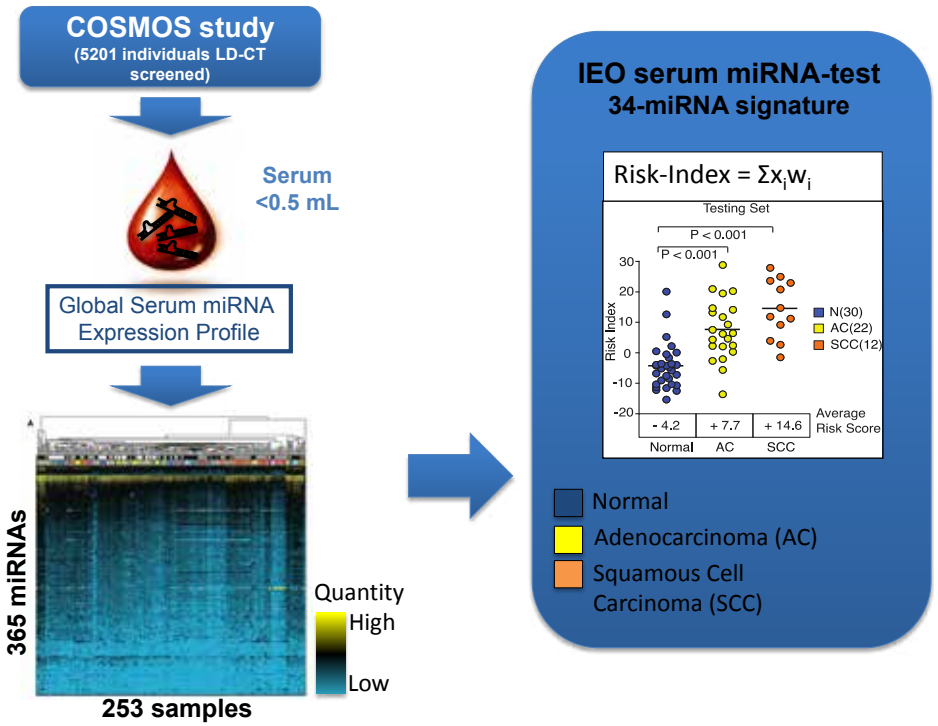

Figure 2 Flowchart of the COSMOS study.

observational trial and we validated selected miRNAs signatures in an independent series of subjects belonging to the randomized MILD trial (25). High-throughput miRNA expression profiles of plasma samples using TaqMan microfluidic cards and single assays for validation studies were performed and, importantly, we generated an original method to analyze data by looking at reciprocal miRNA ratios, an approach that allowed us to bypass the controversial issue of data normalization of miRNA in plasma. In this way, we identified 24 miRNAs whose reciprocal ratios were able to discriminate patients at risk of developing lung cancer and at risk for aggressive disease development in samples collected before disease detection, as well as diagnostic and prognostic signatures in plasma collected at the time of disease detection (*Figure 3*).

In order to have a more friendly and useful tool to classify plasma samples in clinical trials we recently generated a three-level risk categorization for disease: low, intermediate and high miRNA signature classifier (MSC) by combining the different signatures (*Figure 4*) and we used this pre-specified classifier to test diagnostic and prognostic performance in a Clinical Validation Study using the Multicentric Italian Lung Detection (MILD) Trial [2005-2012] cohort.

For this study, 1,000 consecutive plasma samples collected from June 2009 to July 2010 among lung cancer-free individuals enrolled in the trial were used to determine the specificity of the MSC. Plasma samples were first assayed for hemolysis to remove samples from patients that were potentially contaminated by red blood cells miRNAs (26,27).

Of the 1,000 samples, 130 were not evaluable because of hemolysis. Of the remaining 870 subjects, 594 (68%) belonged to the LDCT arms and 276 (32%) to the observational arm. To obtain a cohort for determining the sensitivity performance of MSC, plasma samples from almost all patients with lung cancer diagnosed by September 2012 were obtained (N=85). For 69 of these 85 patients, at least one evaluable sample was collected. For all patients we considered the sample closest to LDCT examination resulting in cancer diagnosis. Specifically, a sample at-diagnosis was available for 50 patients and a pre-disease sample for 19 patients. The pre-disease samples were collected from 8 to 35 months before lung cancer detection with a median lag time of 18 months.

Diagnostic and prognostic performance of MSC

MSC risk groups were examined for all 939 subjects according to lung cancer occurrence, lung cancer death,

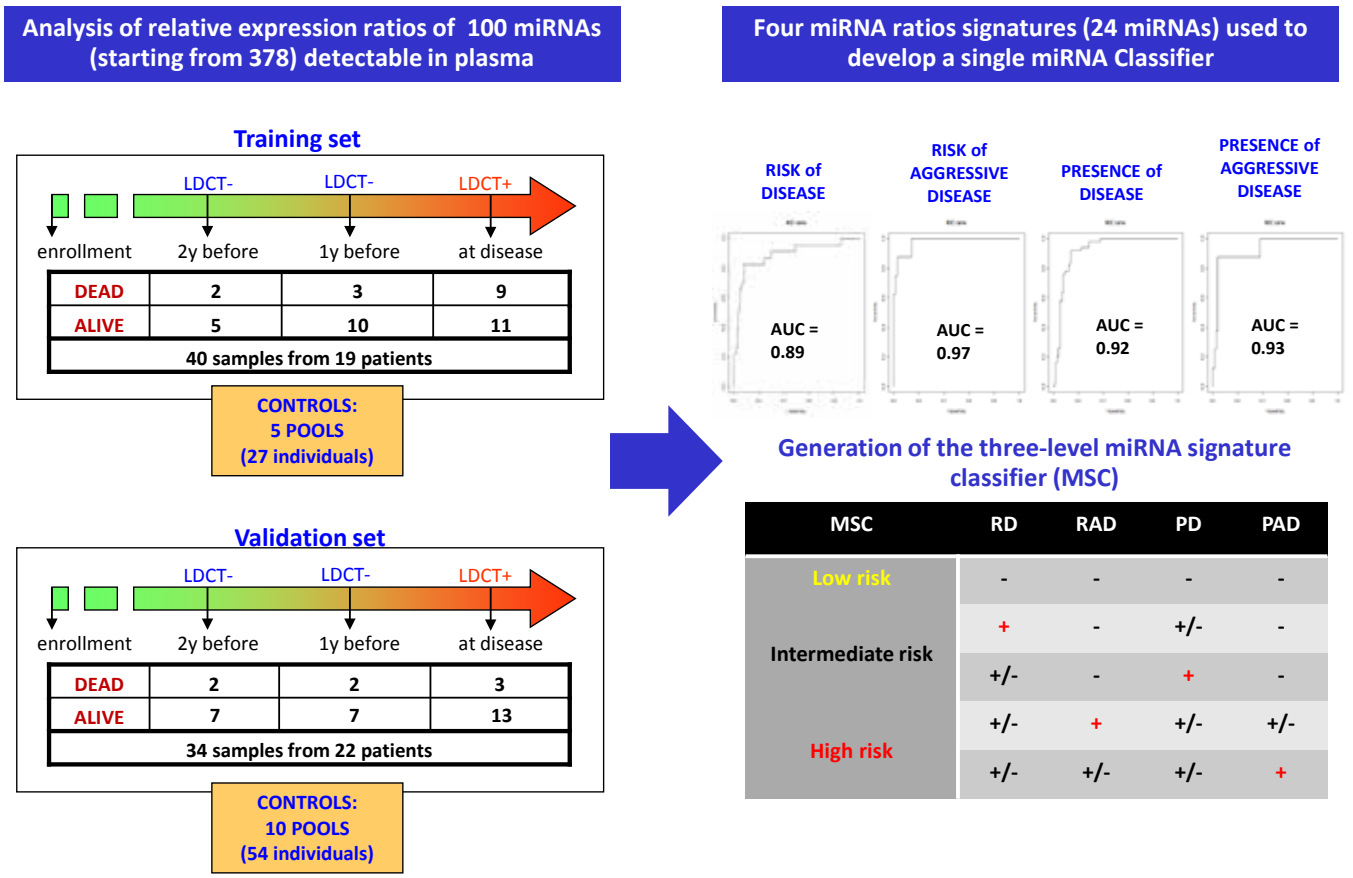

Figure 3 miRNA signatures discovery and initial validation.

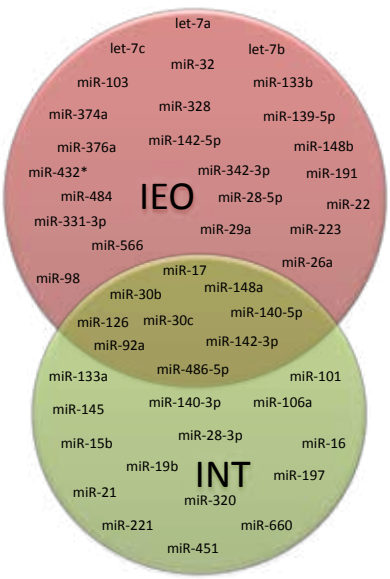

Figure 4 Comparison between serum- (IEO) and plasma-based (INT) miRNA tests.

and tumor stage. MSC Intermediate and High correctly classified 60 of 69 lung cancer patients with 87% SE, 81% SP, 27% PPV and 99% NPV (*Table 3*). MSC risk groups were not significantly associated (P=0.40) with varying tumor stage (I, II-III or IV). No significant differences were observed between MSC risk groups and histological subtypes (χ_1^2=1.60, p=0.4485), and between adenocarcinoma and squamous cell carcinoma (χ_1^2=0.55, P=0.759).

Time dependency analysis of diagnostic performance of MSC, showed similar values of SE, SP, PPV and NPV at 6-, 12-, 18- and 24-month intervals between blood sampling and lung cancer diagnosis supporting a strong diagnostic performance of MSC to predict LC development up to 24 months before disease detection.

Complementary diagnostic performance of LDCT and MSC

Restricting the analysis to the total of 652 subjects in the

Table 3 Overall diagnostic performance of MSC

	Total	MSC (risk of lung cancer)		
		High (%)	Intermediate (%)	Low (%)
All subjects	939	63 (6.7)	159 (16.9)	717 (76.4)
No lung cancer	870	32 (3.7)	130 (14.9)	708 (81.4)
Lung cancer	69	31 (44.9)	29 (42.0)	9 (13.0)

MSC, miRNA signature classifier.

LDCT arm, LDCT identified 46 of 58 lung cancer subjects missing three patients with no pulmonary nodule detected and nine patients because of an interval cancer for a SE of 79%. Pre-specified binary risk groups of MSC (considering High and Intermediate versus Low) identified 40 of 46 LDCT-detected cancers, 8 of 9 interval cancers and all three subjects with "no pulmonary nodule".

LDCT had a SP of 81% for the clinically actionable subgroup of non-calcified nodules >5 mm and an associated false positive rate of 19.4% (115/594). When double-positive (LDCT and MSC) subjects were considered, the false positive rate decreased to 3.7% (22/594), with a decrease in SE (40/58, 69%). On the other hand, MSC detected 9 of 11 (82%) lung cancers that occurred in the observational arm.

The 5-fold reduction in false positives obtained by combining the MSC Lung Cancer assay to the results of the LDCT scan is of great clinical relevance in the context of reducing the false positive rate and the potential side effects associated with repeated LDCT scans or other unnecessary invasive diagnostic follow-ups.

Association of MSC risk groups with survival

The prognostic performance of the three pre-defined MSC risk groups to predict overall survival from plasma samples collected for all subjects with 3-year follow-up (N=939) was also evaluated. Three-year survival was 100%, 97% and 77% for Low, Intermediate and High respectively. The difference in survival between High/Intermediate and Low MSC was statistically significant (χ_1^2=49.53, P<0.0001) also after adjustment for age and gender (χ_1^2=12.57, P=0.0004).

This correlative study in lung cancer is the first of its kind, validating a biomarker using prospectively collected blood samples from a large randomized lung cancer screening trial. In addition to a significant reduction in the rate of false positive results, the performance of the MSC Lung Cancer assay was independent of the stage of lung cancer, as well as the time prior to detection of cancer with LDCT. This suggests additional potential utility for diagnosis and early detection with the MSC Lung Cancer assay.

Comparison between serum and plasma-based miRNA tests

Between the two miRNA signatures developed in serum and plasma, only nine miRNAs were overlapping, suggesting the relevance of this core of miRNAs for early lung cancer diagnosis (*Figure 4*).

The differences in the remaining miRNAs composing the signatures may be likely related to the type of biological samples used (i.e., serum *vs.* plasma) and the study design. In fact, our findings and those reported in literature suggest that miRNAs not released in physiological process, as during the cell lysis that occur during clot formation in serum samples, have a different physical state than miRNAs physiologically released and protected by lipoproteic complex or microvesicles (28,29). Moreover, the plasma signature was trained in samples of patients collected also before (and at the time of) disease detection, thus reflecting earlier, microenvironment-related changes whereas the serum-based signature was trained in serum samples of patients at the time of lung cancer diagnosis likely detecting more advanced tumor-specific changes.

A large validation phases in two different prospective screening trials in ongoing for both miRNA tests.

Conclusions

Early detection candidate biomarkers exist but only few of them are validated or tested in screening settings. The priority is now to validate existing candidates.

Biomarkers should provide knowledge about added value and therefore should be integrated to clinical, laboratory and imaging (LDCT) routine data.

To demonstrate clinical utility requires significant investment in effort and resources towards prospective biomarkers driven clinical trial.

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Footnote

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What do we know about ground-glass opacity nodules in the lung?

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Abstract: Ground-glass opacity nodules (GGNs) in the lung attract clinical attention owing to their increasing incidence, unique natural course, and association with lung adenocarcinoma. A long and indolent course of a GGN makes it difficult to manage. Current extensive clinical, radiological, pathological, and genetic studies on GGNs have shed light on their pathogenesis and allowed development of a reliable strategy of management. The present editorial provides answers to clinical questions related to GGNs, such as the natural course, follow-up, prediction of growth, and resection techniques. Finally, I discuss the etiology of GGNs, which has not been fully elucidated so far.

Keywords: Ground-glass opacity nodules (GGNs); growth; epidermal growth factor receptor (EGFR); lung adenocarcinoma

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The introduction of low-dose chest computed tomography (CT) screening into the clinical practice has led to an increase in the detection rates of lung nodules. A considerable percentage of these nodules are ground-glass opacity nodules (GGNs). The characteristics of patients with GGNs are different from those of patients with typical lung cancer. Patients with GGNs are usually women, nonsmokers, of Asian origin, and relatively young. Most of the papers on GGNs are from Asian countries, especially Japan and Republic of Korea. The management of a GGN is particularly important because its long and indolent course requires frequent CT screening, which may cause high radiation exposure, economic burden, and psychological stress to patients.

As a clinician who has encountered a considerable number of patients with GGNs, I would like to discuss several issues that are clinically important in the management of these patients.

(I) Most clinicians have probably observed that a percentage of GGNs disappear spontaneously (a transient GGN). My research group found that 37% of pure GGNs (pGGNs) and 48% of mixed GGNs (mGGNs) regressed or disappeared within 3 months, which suggested their inflammatory nature (1).

(II) What is the natural course of a persistent GGN? In an actual clinical setting, most GGNs seem to remain unchanged for a long time. Many doctors tend to neglect the clinical importance of GGNs and often report that small GGNs have little clinical significance just like micronodules in the thyroid. Several papers reported long-term follow-up results of patients with GGNs. Hiramatsu *et al.* (2) first reported that 26% of GGNs significantly increased in diameter (over 2 mm of the whole GGN). Matsuguma *et al.* (3) and Kobayashi *et al.* (4) reported that 41% and 29% of mGGNs, respectively, showed significant growth. Two similar Korean studies were also reported. Chang *et al.* reported that 12% of pGGNs increased significantly (5). My group also reported that 26% of GGNs showed a significant increase

and that mGGNs, initial large size, and old age were independent risk factors for growth (6). I believe that the proportions of GGNs that increase in size are higher than most doctors expect.

(III) How long shall we follow up GGNs? Kobayashi *et al*. (4) analyzed 108 GGNs and found that all GGNs showing a significant increase in size grew within 3 years. Therefore, they recommended that patients with GGNs should be followed by clinicians for at least 3 years. I agree that 3 years is the minimum duration of follow-up in these patients. Although it is uncommon to find a GGN grow after long-term standstill, my group revealed that 2 of 90 GGNs (2.2%) followed up for more than 4 years showed significant growth after 4 years (6). Personally, I recommend increasing the interval of CT screening from 1 to 2 or 3 years for a GGN, which does not change during the initial 3-year follow-up.

(IV) Can we predict GGNs that will grow eventually? A considerable proportion of GGNs disappear spontaneously. An ill-defined border of a GGN may be a sign of spontaneous regression, which suggests an inflammatory nature (1,7). Several characteristics of GGNs may be the sign of future growth and malignancy. Initial large size, spiculated border, the presence of bubble lucency, and a history of cancer are generally accepted risk factors for growth and malignant transformation of GGNs. Kobayashi *et al*. (8) analyzed 120 GGNs with the ground glass opacity portion over 50% (solid portion of less than 50%). Large initial size and smoking history were associated with growth. My group also revealed that an initial size over 10 mm, the presence of the solid portion, age over 65 years, and male sex were risk factors for an increase in size (6).

Recently, Kobayashi *et al*. (9) investigated the differences in genetic features of lung adenocarcinoma presenting with GGN with and without growth. They analyzed the mutation or rearrangement of epidermal growth factor receptor (EGFR), K-ras, anaplastic lymphoma kinase (ALK), and HER2 from 104 resected GGNs and analyzed the genetic differences according to the growth status. The EGFR mutation was the most common (64%), followed by K-ras (4%), HER2 (4%), and ALK (3%). The remaining 26 GGNs showed no genetic difference (quadruple negative). Among 104 GGNs, a follow-up thin-section CT was performed in 71 lesions, 30 of which showed growth. Among the remaining 41 GGNs, five lesions were classified as a no-growth group because they were followed up for more than 2 years. Among 25 quadruple-negative GGNs, only 5 were evaluated for growth and one GGN was shown to increase in size. However, among 39 GGNs with the EGFR mutation, 28 GGNs were evaluated for growth and 27 were shown to increase in size. They concluded that EGFR-driven GGNs showed a tendency for growth and quadruple-negative GGNs were associated with no growth. This finding is clinically significant because it shows that the presence of the EGFR mutation, known as driver oncogene of a GGN, is a strong indicator of GGN growth and an indication for surgical resection.

Although Kobayashi *et al*. (9) reported a very important finding, two points have to be mentioned. First, a substantial number of GGNs were not included in the growth analysis because the follow-up period lasted less than 2 years. In particular, only 5 of 26 quadruple-negative GGNs were analyzed. Although the difference was statistically significant, too many data were missing. Second, a genetic analysis of GGNs can be done after surgical resection, and it is difficult to analyze the genetic features of GGNs before surgery. The tissue of a GGN may be obtained using percutaneous transthoracic needle biopsy (PCNB) (10); however, surgical resection without preoperative biopsy is the major strategy in the management of GGNs with high diagnostic accuracy.

(V) When do we recommend surgical resection of a GGN to a patient? Widely recommended indications for biopsy or surgical resection by Fleischner Society include (i) a pGGN of over 15 mm in diameter and (ii) mGGN with a solid portion of 5 mm or more (11). In my opinion, a significant increase in size (over 2 mm) or the appearance of a solid portion may be an indication for resection (12).

(VI) Is it necessary to perform biopsy before resection? I recommend surgical resection rather than needle biopsy because of the following reasons: (i) a high correlation between a CT finding and

pathological finding has been established, such as the correlation of microinvasion in pathology and solid portion of a GGN (13,14); (ii) PCNB may cause some procedure-related complications and takes a long time exposing the performer to high radiation; and (iii) most importantly, introduction of video-assisted thoracoscopic surgery made it easy to remove a GGN without considerable damage to patients. At my institute, we perform resection without PCNB for a GGN if it meets the criteria by Fleischner Society or significant increase in size, and we have reported that 95% of the resected GGNs were malignant (12).

(VII) What is the suitable type of resection for GGNs? Lobectomy is the surgical modality of choice for lung cancer. However, we might ask the question of whether it is necessary to resect one lobe for the resection of a GGN of 10 to 20 mm in size. Many institutes performed limited (sublobar) resection such as segmentectomy or wide-wedge resection for GGNs and reported similar results to those obtained with standard lobectomy (15). Limited resection is preferred to lobectomy because it saves pulmonary function (16). However, lobectomy is still indicated for GGNs with over 25% of the solid portion (15).

(VIII) Another important issue related to GGNs is multiplicity. Roughly, one-third of patients with a GGN have more than two GGNs simultaneously or one after another. According to the current staging system, if two or more malignant nodules are found in the same lobe, it would be T3 and if in a different lobe, it would be T4. Furthermore, if nodules were in a different lung, it would be M1a. This staging system would be correct if we consider that all multiple GGNs were metastatic nodules. Usually, multiple GGNs are all similar in size and are found in different lobes or lungs. My group analyzed the genetic features (EGFR and K-ras) of multiple GGNs resected from the same patients. The analysis of the EGFR mutation showed that high frequency of discordant EGFR mutations (17 of 24, 70.8%) could discriminate tumor clonality (18 of 24, 75%) of multiple lung neoplastic nodules presenting as GGNs (17). Therefore, multiple GGNs seem to be multifocal in origin rather than being intrapulmonary metastasis.

This finding could provide a rationale for the current strategy of surgical resection of dominant GGNs in patients with multiple GGNs (18,19).

(IX) The final question related to GGNs concerns the etiology. There are several differences between lung cancer with a GGN and typical lung cancer. A GGN is not associated with smoking unlike smoking-related lung cancer. GGNs occur at a relatively young age. Moreover, they develop in the peripheral portion of the lung and many of them show a multifocal origin. Some researchers suggested cooking fumes as a causative agent; however, there is no clear evidence to support this hypothesis. Recently, a multicenter epidemiological study of nonsmoker lung cancer has been launched in Republic of Korea. I strongly believe that it will help elucidate the etiology of a GGN.

In conclusion, a GGN is a unique type of lung cancer or a precancerous lesion characterized by a long and indolent course. Regular follow-up and the determination of the type of surgical resection are particularly important because a considerable proportion of GGNs progress into invasive adenocarcinomas, usually driven by the EGFR mutation. Understanding the etiology of GGNs would help prevent their formation and would allow us to develop novel management strategies.

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Footnote

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Pulmonary ground-glass opacity: computed tomography features, histopathology and molecular pathology

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Abstract: The incidence of pulmonary ground-glass opacity (GGO) lesions is increasing as a result of the widespread use of multislice spiral computed tomography (CT) and the low-dose CT screening for lung cancer detection. Besides benign lesions, GGOs can be a specific type of lung adenocarcinomas or their preinvasive lesions. Evaluation of pulmonary GGO and investigation of the correlation between CT imaging features and lung adenocarcinoma subtypes or driver genes can be helpful in confirming the diagnosis and in guiding the clinical management. Our review focuses on the pathologic characteristics of GGO detected at CT, involving histopathology and molecular pathology.

Keywords: Ground-glass opacity (GGO); computed tomography (CT); pathology; driver genes; epidermal growth factor receptor gene (*EGFR*); anaplastic lymphoma kinase gene (*ALK*); Kirsten rat sarcoma viral oncogene homolog (*KRAS*)

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Introduction

Pulmonary ground-glass opacity (GGO), is defined as hazy opacity that does not obscure underlying bronchial structures or pulmonary vessels at high-resolution computed tomography (HRCT) (1). The detection and recognition of GGO is based on a subjective assessment of lung attenuation at CT, therefore, CT should be performed within objective parameters that make lesion depiction reliable and reproducible (2). These lesions include both benign and malignant lesions such as focal interstitial fibrosis, inflammation, hemorrhage, or lung adenocarcinoma and their preinvasive lesions (3,4). Many studies have reported that preoperative CT scan findings are related to pathological features and postoperative prognosis (5-7).

Lung adenocarcinoma is the most common histologic subtype of lung cancer and shows high heterogeneity at histology and cellular level (8,9). In 2011, the International Association for the Study of Lung Cancer, American

Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) have proposed a new classification for lung adenocarcinoma, refining its classification, which emerged into a better standard of clinical treatments (10). This new classification is of stage-independent prognostic and also of high predictive value for adjuvant treatment (11,12) and was most recently incorporated into the new 2015 WHO classification (13). Furthermore, lung cancer and especially lung adenocarcinoma, with specific mutations or rearrangements in genes such as EGFR, KRAS, and ALK, may show different tumor sensitivities to targeted therapeutic agents. Therefore, it is desirable to be aware of the correlations between GGO pattern and pathology subtypes and/or expression of driver genes.

Histopathology and CT features

Pulmonary GGO nodules can be observed in benign conditions, including focal interstitial fibrosis, inflammation, and hemorrhage, as well as in preinvasive lesions such as atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), or in malignancies such as minimally invasive adenocarcinoma (MIA), lepidic-predominant invasive adenocarcinomas (LPA) (10,14).

Focal interstitial fibrosis

Focal interstitial fibrosis represents the main entity among benign GGO (3). At histopathologic analysis, tissue specimens show interstitial septal thickening with fibroblast proliferation and preservation of the intra-alveolar airspace (15); if solid components are present, they may be related to the presence of fibrotic foci and alveolar collapse (16). Although recognized as benign entity, focal interstitial fibrosis shares many CT features with neoplastic diseases, and its differentiation from a malignant lesion is mainly based on its stability over time.

Inflammation

Inflammation showing as GGO, can be related to any kind of infectious pneumonia, but it is a more frequent presentation for cytomegalovirus (CMV) and Pneumocystis jirovecii CT findings of CMV infection may include GGO, dense consolidation, bronchial wall thickening or bronchiectasis, and interstitial reticulation without air-space disease (17); CT findings for Pneumocystis jirovecii infection may include the presence of an isolated ground-glass infiltrate without additional findings in the proper clinical setting (18).

Pulmonary hemorrhage

Pulmonary hemorrhage can be diffuse, patchy, or focal, depending on the underlying cause. Pulmonary-renal syndromes that may cause pulmonary hemorrhage include Goodpasture's syndrome, Wegener's granulomatosis, systemic lupus erythematosus, Henoch-Schonlein purpura, mixed connective-tissue disease, and other vasculitis (14). Other causes of pulmonary hemorrhage include anticoagulant therapies, disseminated intravascular coagulation, thrombocytopenia, leukemia, acute lung injury, aspiration of blood, drug toxicity, traumas, and mitral stenosis (19). CT scans may show consolidation with GGO and interlobular septal thickening, as well as a halo of GGO around a focal area of lung consolidation.

GGO can be observed not only in presence of benign conditions but also in preinvasive lesions or in malignancies.

AAH

AAH is defined as a localized, small usual pneumocytes and/or Clara cells lining the alveolar walls and respiratory bronchioles (20). On chest CT, AAH is characteristically shown as a small pure GGO, usually measuring <5 mm, but a few can reach 12 mm. Lesions may be single or multiple with low density. Several authors have reported that AAH may be a precancerous lesion or a putative precursor of well-differentiated adenocarcinoma of the lung (21).

In 2011, IASLC, ATS and ERS proposed a new classification for lung adenocarcinoma, which is now included in the official 2015 WHO classification, that included a number of changes to previous classifications, which now considers resection specimens, small biopsies, and cytology specimens (10). For resection specimens, the new terms of AIS and MIA are introduced for small adenocarcinomas, which show pure lepidic or predominantly lepidic growth, with invasion ≤5 mm, respectively. Invasive adenocarcinomas are now classified with a newly added semi-quantitative pattern analysis, a micropapillary pattern, except lepidic, acinar, papillary, and solid by their predominant pattern. This classification also provides guidance for biopsies and cytology specimens.

AIS

AIS is a localized small by their predominant pattern. This classification also provides guidance for biopsies and cytology specimen lepidic growth that lack stromal, vascular, or pleural invasion. AIS was defined as a preinvasive lesion. On CT, nonmucinous AIS appears typically as a pure GGO (22). The pure GGO of AIS usually appears on thin-

section CT as slightly higher attenuation compared with the very faint GGO of AAH (23,24). AIS can also be either single or multiple (25).

MIA

MIA is a small, solitary adenocarcinoma (ltiplein-section CT as slight lepidic pattern and invasion carcinoma) (26). A provisional description of nonmucinous MIA on thin section CT is a part-solid nodule consisting of a predominant ground-glass component and a small solid component measuring 5 mm or less (27). Mucinous MIA can appear as a solid or part-solid nodule (28). There is an overlap among imaging features of AAH, AIS, and MIA. MIA was more often a larger, lobulated or irregular, mixed ground-glass nodule with a solid component larger than 5 mm, and a higher attenuation value (29).

LPA

LPA, a subtype of invasive adenocarcinoma, is defined as nonmucinous adenocarcinomas previously classified as a mixed subtype in which the lepidic component is predominant. A diagnosis of LPA rather than MIA can be made if the tumor contains >5 mm of a histologic subtype other than a lepidic pattern (i.e., acinar, papillary, micropapillary, or solid) or >5 mm of myofibroblastic stroma with invasive tumor cells; or invades lymphatics, blood vessels, or pleura; or contains tumor necrosis. Consequently, on CT, it can be shown as a part-solid opacity with variable proportions of ground-glass and solid components (10), usually described as a prevalent GGO nodule, with a solid component >5 mm. In general, other subtypes of invasive adenocarcinomas such as acinar, papillary, micropapillary and solid predominant lesions rarely show GGO at HRCT.

A careful evaluation of the CT features of nodular GGO in neoplastic disease may help in assessing the disease prognosis. Indeed, in a retrospective review, after surgery AAH and AIS had 100% 5-year disease-free survival, respectively; MIA had almost 100% 5-year disease-free survival. The 5-year disease-free survival of invasive adenocarcinoma, as for example when a nodular GGO lesion with a predominant solid portion is accompanied by CT features such as spiculations, pleural retraction, or bronchovascular bundle thickening, is significantly reduced (16), likely because such lesions are associated with higher probabilities of lymph node metastasis and vascular invasion (30). The sub-classification of invasive adenocarcinoma has prognostic import as well, since solid and micropapillary predominant lesions have a poor prognosis, while papillary and acinar adenocarcinoma have an intermediate prognosis and LPA have a favorable prognosis (11).

Currently, only a pathological assessment can ascertain if a GGO is benign or malignant. However, the clinical setting and a careful assessment of changes of the GGO appearance at CT over time, may enable an accurate suggestion of diagnosis. It is indeed known that most benign conditions resolve spontaneously or after appropriate treatment over weeks or months, and patients have characteristic clinical findings and symptoms (14). In contrast, malignant neoplasms are persistent, and their size and attenuation may increase over several months or years, usually in absence of clinical symptoms (14).

For this reason, management of GGO detected at CT for lung cancer screening is usually based on their re-evaluation. In 2016, the National Comprehensive Cancer Network (NCCN) made the latest guidelines (version 1, 2017) for lung cancer screening (31).

For solid nodules: nodules less than 6 mm can only accept ongoing annual screening. On the other hands, if the nodules are in 6 to <8 mm, they are recommended to undergo a repeat low-dose CT in 6 months. If the nodules become stable, repeated at 6 months, and if continued stable, reverting to annual screening. Nodules ≥8 mm are to be considered for PET. If the clinical, radiologic, and PET findings suggest a suspicion of lung cancer, the patients need biopsy or surgical excision. Otherwise, if the nodules are low suspicion for lung cancer, then they would be followed with a low-dose CT in 3 months, and if stable, a follow-up CT 6 months later, and if still stable, reverting to annual follow-up imaging.

For part-solid nodules: nodules less than 6 mm can only accept ongoing annual screening. If the nodules are in ≥6 mm with solid component <6 mm, they are recommended to undergo a repeat low-dose CT in 6 months, and if continued stable, reverting to annual screening. Nodules with solid component ≥6 mm are to be considered for PET. If the clinical, radiologic, and PET findings suggest a suspicion of lung cancer, the patients need biopsy or surgical excision. Otherwise, if the nodules are low suspicion for lung cancer, then they would be followed with a low-dose CT in 3 months. If still stable, nodules with solid component 6 to <8 mm are to be reverting to annual follow-up imaging, and nodules with solid component ≥8 mm are recommended to undergo a repeat low-dose CT in 6 months, and if continued stable, reverting to annual

follow-up imaging.

For non-solid nodules: nodules less than 20 mm are followed simply with routine annual low-dose CT. However, if these nodules have increased in size or have developed a solid or part solid component in follow-up, then they would undergo either escalated interval follow-up low-dose CT in 3 to 6 months, biopsy, or surgical excision. Nodules ≥20 mm are recommended to undergo a follow-up low-dose CT in 6 months. If the nodules become stable, repeated at 6 months, and if continued stable, reverting to annual screening. If they increase in size or become solid or part-solid, then they are recommended to undergo either repeat low-dose CT in 6 months, biopsy, or surgical excision because of the high suspicion of adenocarcinoma or AIS.

In this guidelines, the definition of nodule growth is as follows: (I) for nodules 15 mm or smaller: an increase in mean diameter of 2 mm or more in any nodule or in the solid portion of a part-solid nodule when compared with the baseline scan; or (II) for nodules 15 mm or lager: an increase of 15% in mean diameter when compared with the baseline scan. Mean diameter is the mean of the longest diameter of the nodule and its perpendicular diameter (31). Although this NCCN algorithm is very useful, of course, clinical scenarios should make precise therapeutic regimens of pulmonary nodules according to the actual situation of patients, improving the survival of early lung cancer and diagnosis level.

Molecular pathology and CT features

Recent practice guidelines in oncology and pathology recommend that all locally advanced and metastatic NSCLC with adenocarcinoma histology undergo testing for the most common targetable genetic abnormalities, such as epidermal growth factor receptor gene (*EGFR*) mutations, anaplastic lymphoma kinase gene (*ALK*) rearrangements, and non-targetable such as Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations (32).

To date, several studies, mostly in Japan, China and Republic of Korea, have investigated the association between CT imaging features and driver genes such as *EGFR*, *ALK*, and *KRAS*. Most reports focused on the presence of any GGO or GGO proportion and some of the findings are conflicting. The definition of GGO proportion differs among studies and the following parameters have been used to calculate the GGO proportion: consolidation/tumor dimension ratio (33,34), GGO/tumor area ratio (35), area ratio of tumor on mediastinal windows to that on lung windows, GGO/tumor volume ratio (6,36,37), and the product of the dimension ratio of the tumor on mediastinal windows to that on lung windows to calculate the tumor shadow disappearance rate (TDR) (37-39).

Yano *et al*. (40) demonstrated that *EGFR* mutations were found more frequently in small peripheral adenocarcinoma with a diameter <3 cm and with a GGO ratio ≥50%, especially among women. Sugano *et al*. (33) examined the presence of GGO and *EGFR* mutations in 136 patients with surgically resected primary lung adenocarcinoma. Although no significant association was found between GGO and *EGFR* mutations (P=0.07), the *EGFR* mutation occurred more frequently in male patients with GGO than in those without GGO. Furthermore, two studies (41,42) involving 263 and 285 lung adenocarcinoma, reported that the *EGFR*-mutated group had significantly higher frequencies and no higher frequencies of GGO, respectively. Lee *et al*. (6) found that GGO volume percentage in tumors with L858R mutation was significantly higher than that in *EGFR* wild-type tumors (P=0.0001) and 19 deletion mutated tumors (P=0.0006). A significant trend of prevalence of L858R mutation increasing along with increasing GGO volume percentage (P=0.0001) was found. Discordant to Lee *et al*.'s report, Yang *et al*. did not find a significant correlation of GGO volume ratio with L858R mutation, but with 19 deletions (36), while Hong *et al*. (34) found that GGO ratio in tumors with either exon 19 deletions or L858R mutation, was significantly higher than that in *EGFR* wild-type tumors (P=0.009 and 0.029, respectively). Based on the abovementioned studies, we may assume that the presence of GGO or higher GGO ratio may be associated with higher frequencies of *EGFR* mutation. However, the association between GGO and *EGFR* mutation is still debated because of conflicting results of different studies (39,43-45). These controversial results may be the result of different ethnicity, grouping methods, measurement of GGO ratio, sample size and inclusion criteria among studies.

Besides *EGFR* mutation status, a few studies investigated the association between GGO and *EGFR* copy number or protein overexpression. *EGFR* amplification were inversely correlated with the GGO percentage, indeed the frequency of FISH-positivity increased as the proportion of GGO decreased (6,46,47).

There are limited numbers of reports focusing on *KRAS* mutations or *ALK* rearrangements. Most studies found no significant association between *KRAS* mutations and presence

of any GGO (43,44,48) or GGO ratio (33). One study (45) revealed that *KRAS* mutations were more common in lesions with a lower GGO proportion. Zhou *et al*. (37) compared the radiologic characteristics of lung adenocarcinomas with presence or absence of *ALK* rearrangements and *EGFR* mutations. They demonstrated that the percentages of GGO volume and TDR were significantly lower in the *ALK* rearrangements group than the *EGFR* mutation group and the wild type group, which was consistent with the study by Fukui *et al*. (49). In their analysis, the mean TDRs were significantly lower in the *ALK* rearrangement positive group (P=0.0006). Furthermore, evaluation of imaging findings of 36 cases with advanced *ALK*-positive NSCLC showed a prevalence of solid pattern of growth, without GGO (50). These features might suggest that they have a more invasive nature than those with more GGO components. Generally, ALK rearrangement is rare in lung adenocarcinoma presenting as GGOs and is associated with a more advanced stage and larger tumor size (38).

Concerning the GGO change patterns, Aoki *et al*. (51) evaluated 25 lung adenocarcinomas <3 cm with GGO (>50%): tumor size increased in 19 of 25 adenocarcinomas during the observation period and the GGO changes in 19 patients were classified into four patterns: persistent pure GGO, change from pure to mixed GGO, mixed GGO with growth of solid component, and mixed GGO with growth of GGO component. *EGFR* mutations were found in all four patterns and were not correlated with GGO change patterns. Accordingly, another study (52) involved 23 lung adenocarcinomas and classified patterns of radiological changes into three groups: pure GGO without consolidation; appearance or increase in consolidation within pure GGO; consolidation without pure GGO. There was no trend between *EGFR* mutations and patterns of radiological changes during the follow-up period. Interestingly, both studies reported that inactivation of p53 may be associated with the appearance or growth of central consolidation within pure GGO. In a recent study (53), 104 GGO nodules <3 cm with ground-glass component >50% were evaluated for the presence of *EGFR*/*KRAS*/*ALK*/*HER2* mutations and growth, defined as ≥2 mm increase in diameter or appearance of a solid component. Among the 71 lesions evaluated for growth, *EGFR* mutation was correlated with growth, whereas quadruple-negative tumors were significantly associated with no-growth.

The relationship of gene mutation status and the presence of multiple GGO lesions in lung adenocarcinoma were seldom studied. In 2009, Chung *et al*. (54) examined 56 multiple pulmonary nodules presented as GGO in 24 patients, to assess if the mutation status of EGFR and *KRAS* genes correlates with radiological features. A total of 17 patients showed different *EGFR* gene expression in their multifocal lesions, and only 7 patients had identical gene status without any mutation. *KRAS* gene mutation also showed asymmetric fashion in multiple lesions. Combining both *EGFR* and *KRAS* gene alterations, 75% of the patients had heterogeneous genetic status in their multiple lesions. Two recent studies also reported the heterogeneity among multiple GGOs. One analyzed for mutations in *EGFR*, *KRAS*, *HER2*, *BRAF*, and *PIK3CA* together with fusions in *ALK*, *ROS1*, and *RET*. The discordance rate of driver mutations was 80% in those patients harboring at least one of the detected driver mutations (55). The other (56) focused on subtypes of *EGFR* mutation and reported a discordance rate of 92.1%. These results suggest that multiple GGO lesions in lung adenocarcinoma may have a different origin. However, sequential or multiple biopsies to identify subclones can rarely be implemented in routine clinical care.

Future possibilities of evaluation of GGO: radiomics and liquid biopsies

New tools under consideration for evaluation of lung nodules, including GGO, are radiomics and liquid biopsies.

Radiomics is an emerging field that converts imaging data into a high dimensional mineable feature space using a large number of automatically extracted data-characterization algorithms. These imaging features capture distinct phenotypic differences of tumours and may have prognostic power and thus clinical significance across different diseases (57). Indeed, quantitative image features based on intensity, shape, size or volume, and texture offer information on tumor phenotype and microenvironment (or habitat) that is distinct from that provided by clinical reports, laboratory test results, and genomic or proteomic assays. These features, in conjunction with other (clinical) information, can be correlated with clinical outcomes data and used for evidence-based clinical decision support.

Furthermore, liquid biopsy analysis has become a new opportunity in translational cancer research and in clinical practice (58). Genetic profile of tumors is currently obtained from surgical or biopsy specimens, but biopsy represents a spatial and temporally limited snap-shot of a tumor. It has been shown that the initial surgical specimen might significantly differ from the molecular profile of its metastases (59). Moreover, the initial biopsy might not

reflect tumor heterogeneity and sequential biopsies can rarely be implemented in routine clinical care because of ethical, financial or logistical barriers. Liquid biopsies offer prognostic and predictive information, obtained by a minimally invasive, inexpensive and easily obtainable technique, where circulating tumor cells (CTC) and cell-free DNA (cfDNA) can be evaluated for the presence of genetic mutations/aberrations from a single blood sample.

Conclusions

In conclusion, it is important to understand the relationship between CT radiologic features of GGO and lung adenocarcinoma subtypes, according to the 2015 WHO classification standard. Furthermore, understanding the association of the presence of GGO, or GGO ratio, and molecular biomarkers, can guide targeted treatments, especially when a biopsy tissue or surgical specimen is not available.

In the near future we do expect that adjunctive tools will be able to help guiding the choice of treatment, will be radiomics and liquid biopsies.

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Footnote

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Management of ground-glass opacities: should all pulmonary lesions with ground-glass opacity be surgically resected?

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Abstract: Pulmonary nodules with ground-glass opacity (GGO) are frequently observed and will be increasingly detected. GGO can be observed in both benign and malignant conditions, including lung cancer and its preinvasive lesions. Atypical adenomatous hyperplasia and adenocarcinoma in situ are typically manifested as pure GGOs, whereas more advanced adenocarcinomas may include a larger solid component within the GGO region. The natural history of GGOs has been gradually clarified. Approximately 20% of pure GGOs and 40% of part-solid GGOs gradually grow or increase their solid component, whereas others remain unchanged for years. Therefore, it remains unclear whether all pulmonary lesions with GGO should be surgically resected or whether lesions without changes may not require resection. To distinguish GGOs with growth from those without growth, a 3-year follow-up observation period is a reasonable benchmark based on the data that the volume-doubling time (VDT) of pure GGOs ranges from approximately 600 to 900 days and that of part-solid GGOs ranges from 300 to 450 days. Future studies on the genetic differences between GGOs with growth and those without growth will help establish an appropriate management algorithm.

Keywords: Follow-up; ground-glass opacity (GGO); limited surgery; lung cancer; small lung lesion; volume doubling time (VDT)

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Introduction

Ground-glass opacity (GGO) is a radiological finding in computed tomography (CT) consisting of a hazy opacity that does not obscure the underlying bronchial structures or pulmonary vessels (1). Pure GGOs are those with no solid components, whereas part-solid GGOs contain both GGO and a solid component. Pulmonary nodules with GGO have been increasingly encountered in routine clinical practice with the increasingly widespread use of CT and the increased resolution of CT imaging. The recent positive results of the National Lung Screening Trial, which reported a 20% decrease in mortality from lung cancer as a result of low-dose CT screening for patients at high risk of developing lung cancer (2), are anticipated to support the use of CT examinations and to increase the detection of GGO lesions.

GGO can be a manifestation of a wide variety of clinical features, including malignancies and benign conditions, such as focal interstitial fibrosis, inflammation, and hemorrhage (3). However, lesions with GGO that do not disappear are often lung cancer or its precursor lesions (4). Favorable prognoses for the surgical resection of lesions with a considerable amount of GGO have been reported in several retrospective studies, in which the relapse rate was reported to be null (5-8).

Because some lesions with GGO remain unchanged for years, it is unclear whether all such lesions should be surgically resected, including those that microscopy shows to contain cancer cells. It has also not yet been established which surgical procedures are well-balanced. In this article,

we review the literature on GGO, with special emphasis on management of GGO-predominant pulmonary lesions.

Pathological features of lesions with GGO

Noguchi's classification

In 1995, Noguchi *et al.* reviewed 236 surgically resected small peripheral adenocarcinomas ≤2 cm in diameter and proposed a histologic classification of 6 types based on tumor growth patterns (9). Type A, localized bronchioloalveolar carcinoma (BAC), revealed the replacement of alveolar-lining epithelial cells with a relatively thin stroma. Type B was characterized by localized BAC with focal structural collapse of alveoli. Type C was characterized by localized BAC with foci of active fibroblastic proliferation. Type D (poorly differentiated adenocarcinoma), Type E (tubular adenocarcinoma) and Type F (papillary adenocarcinoma) showed compressive and expanding growth. Types A and B showed no lymph node metastasis and had a better 5-year survival rate (100%) than did Type C (75%) or Types D, E, and F (52%). According to Noguchi's classification, GGO can be found in Type A, B and C tumors that show a replacement growth pattern along the alveolar lining cells; for example, Yang *et al.* reported that the proportion of GGO in each of these tumor types was 92%, 52%, and 20%, respectively (10).

New international multidisciplinary classification of lung adenocarcinoma

In 2011, the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) proposed a new international multidisciplinary classification of lung adenocarcinoma (11). The terms BAC and mixed subtype adenocarcinoma are no longer used because these terms were applied to a broad spectrum of tumors. Adenocarcinomas are classified as preinvasive lesions [including atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS)], minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma. AAH is a localized small proliferation of atypical Type II pneumocytes and/or Clara cells lining the alveolar walls and respiratory bronchioles. AIS is a small (≤3 cm) solitary adenocarcinoma with pure lepidic growth, and the complete resection of AIS achieves 100% disease-specific survival. AIS corresponds to Types A and B in Noguchi's classification. MIA is a small (≤3 cm) solitary adenocarcinoma with a predominantly lepidic pattern and ≤5 mm invasion at the largest dimension. MIA does not invade lymphatics, blood vessels, or the pleura and contains no necrosis; therefore, complete resection achieves nearly 100% disease-specific survival. MIA roughly coincides with Type C in Noguchi's classification. In general, lung adenocarcinomas are thought to follow a linear multistep progression whereby AAH progresses to AIS, which is followed by invasive adenocarcinoma.

To discuss the association between the radiological findings of GGO and the pathological diagnosis based on the new IASLC/ATS/ERS classification, we present the updated data from our previous study on lesions with GGO. The inclusion criteria for the study were the following: (I) a lesion diameter ≤3 cm; (II) a GGO proportion >50%; and (III) observation without treatment in the prior 6 months (12). To date, 32 of the 120 lesions were surgically resected. The histological diagnoses were AAH in 3 lesions, AIS in 12, MIA in 11, and invasive adenocarcinoma in 6.

The correlation between the changes in size and the histological types is shown in *Figure 1*. None of the 3 AAHs increased in size, whereas some of the tumors belonging to the types other than AAH did so. From these observations, it is impossible to determine histopathologic types by changes in lesion size.

The association between the radiological findings at the time of the resection and the pathological types is shown in *Figure 2*. The solid component proportions were categorized as 0%, 1%~25%, 26%~50%, and 51%~100%. Preinvasive lesions, including AAH and AIS, are typically manifested as pure GGOs, whereas more advanced adenocarcinomas may include a larger solid component within the GGO region.

Genetic features of lesions with GGO

Several reports have examined the relationship between pulmonary nodules with GGO and the relatively high frequency of epidermal growth factor receptor (EGFR) mutations. In a study of 38 patients with adenocarcinoma, the frequencies of GGO in patients with EGFR mutation and wild-types were 74% and 57%, respectively (13). In another study of 153 patients with adenocarcinoma, the GGO volume percentage in tumors with exon 21 mutation (61.7%±31.9%) was significantly higher than that in EGFR wild-type tumors (30.0%±38.5%) (14). However, the frequencies of

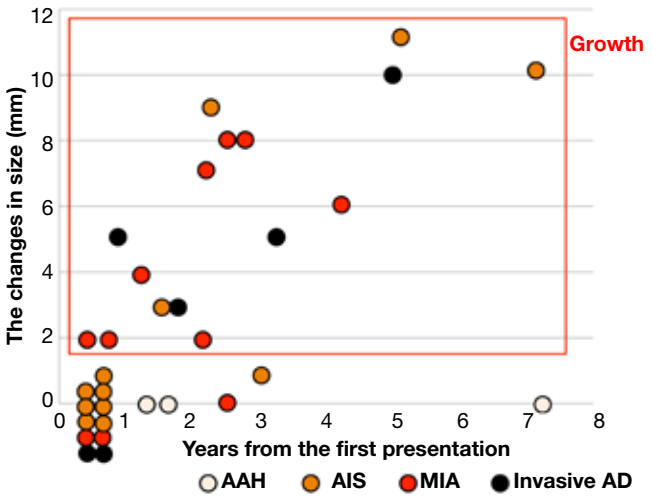

Figure 1 The correlation between the changes in size from the first presentation to the last CT examination and the histological types. AAH existed only in the no-growth group, whereas the remaining histological types existed in both groups.

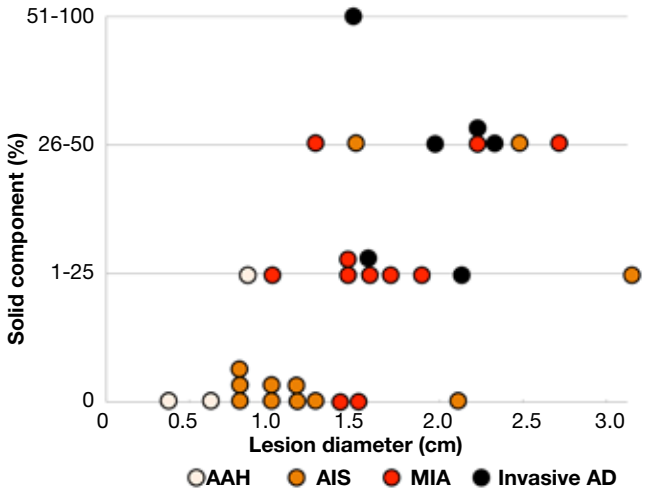

Figure 2 The association between the radiological findings at the time of resection and the pathological types. Solid component proportions are categorized as 0%, 1%~25%, 26%~50%, and 51%~100%. The tendency toward pathological invasiveness is shown, along with the consistent increases in both the size and the solid component.

EGFR mutation did not significantly differ (25%, 36%, 86%, to 67% in AAH, AIS, MIA, and well-differentiated adenocarcinomas, respectively) (15). Both GGO and EGFR mutations are associated with adenocarcinoma histology, female gender, and nonsmoking status.

In comparison, the incidence of KRAS mutations was 33%, 12%, 8%, and 0% in AAH, AIS, MIA, and well-differentiated adenocarcinomas, respectively, in one report (15). The overall frequency of KRAS mutations in lung adenocarcinoma was limited to 13% (16). These findings cannot be explained without assuming that some tumors with KRAS mutations might undergo regression.

The association between radiological findings of GGO and pathological invasiveness

The accuracy rate of a CT-guided core needle biopsy for nodules with GGO depends on the lesion diameter and the proportion of the GGO component; it ranges from 64.6% to 93% (17-19). Recent CT fluoroscopy-guided biopsy has a higher accuracy rate ranging from 82% to 97% (20-22). Of course, we should interpret these results in light of a possible publication bias. The article on the new IASLC/ATS/ERS classification states that AIS and MIA should not be diagnosed in small biopsies or cytology specimens and that if a noninvasive pattern is present in a small biopsy, it should be referred to as a lepidic growth pattern (11). Therefore, diagnosis usually depends on radiographic findings, which correlate closely with the pathologic diagnosis in the determination of treatment options, including surgery.

A GGO proportion of 50% or more is suggested as a cutoff value for pathological noninvasiveness in each lesion size category (*Table 1*) (23-28). In lesions ≤3 cm with a GGO component <50%, the rate of lymph node metastasis ranges from 10% to 26% (23-28). Based on these data, in this article, we mainly address pulmonary nodules with GGO proportion >50%.

When pathological invasiveness is defined as the presence of vascular and lymphatic invasion and lymph node metastasis, the specificity of pathological invasiveness was 100% if the cut-off value was set as a consolidation/maximum tumor diameter (C/T) ratio of ≤0.5 for lesions ≤3 cm (29). There has only been one multi-institutional prospective study to predict pathological noninvasiveness. Based on the analysis of 545 patients, Suzuki *et al.* reported that the specificities for the diagnosis of pathological invasiveness were 96.4% for an adenocarcinoma ≤3 cm with a C/T ratio ≤0.5 and 98.7% for an adenocarcinoma ≤2 cm with a C/T ratio ≤0.25 (30). They concluded that radiological diagnosis of noninvasive lung cancer corresponded well with pathological invasiveness, and radiological noninvasive lung adenocarcinoma could be

Table 1 The association between GGO proportion and pathological invasiveness

First author [year] (references)	Lesion size (cm)	GGO proportion (%)	Total number	LN metastasis [%]	ly	v	pl
Asamua [2003] (23)	≤1	≥50	28	0	2*		–
		<50	20	3 [15]	7*		–
Ikeda [2004] (24)	≤2	≥50	44	0	–	–	–
		<50	115	12 [10]	–	–	–
Suzuki [2006] (25)	≤2	≥50	116	1 [0.9]	2	2	3
		<50	233	46 [20]	94	91	52
Aoki [2001] (26)	≤3	>50	24	1 [4]	–	3	–
		≤50	103	24 [23]	–	49	–
Matsuguma [2002] (27)	≤3	>50	26	0	0	1	–
		≤50	70	18 [26]	18	22	–
Nakata [2005] (28)	≤3	≥50	68	0	–	1	–
		<50	78	16 [21]	–	46	–

LN, lymph node; ly, lymphatic invasion; v, vascular invasion; pl, pleural invasion; *, lymphatic invasion or vascular invasion.

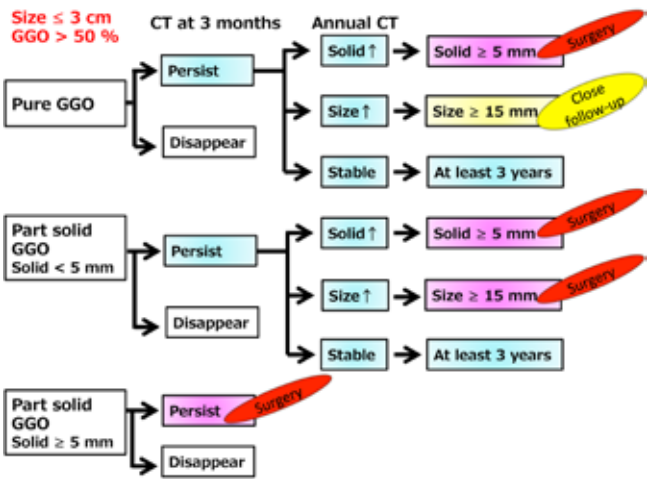

Figure 3 Conservative follow-up algorithm for pulmonary lesions ≤3 cm with a GGO component >50%. Currently, lesions a with solid component ≥5mm are recommended for resection. Pure GGOs ≥15 mm should be closely followed because of the tendency to grow. Part-solid GGOs ≥15 mm should be resected even if the solid component is <5 mm. All of the lesions without changes in the size and solid component should be followed for at least 3 years to accurately evaluate the tendency to grow.

defined as an adenocarcinoma ≤2 cm with a C/T ratio ≤0.25.

Appropriate timing for the decision to surgically resect

Because GGO-predominant lesions include malignancies, we must decide whether to resect at the first presentation. If the lesions were conservatively observed with CT examinations, we must decide when to resect them.

Recently, the Fleischner Society proposed recommendations for the management of GGOs (31). Briefly, they suggested that biopsy or surgical resection should be considered if the solid component becomes 5 mm or more.

The Japanese Society of CT Screening recommends that lesions with GGO ≥15 mm or a solid component ≥5 mm should be resected or biopsied (32).

Considering the Fleischner Society and the Japanese Society of CT Screening recommendations, we propose a conservative follow-up algorithm for pulmonary lesions ≤3 cm with a GGO component >50%, as illustrated in *Figure 3*.

Observation with CT examinations for lesions with GGO

Natural history of GGO

It is essential to understand the natural history of GGOs to discuss the conservative follow-up of GGO. Several reports have revealed that some lesions with GGO exhibit gradual growth, whereas others persist for years without changes (33-36). Representative CT images are presented in *Figure 4*. Recently, 5 reports analyzing more than 100 nodules with GGO have been published, and the results are summarized in *Table 2* (12,37-40). Our study is among these reports, and our results are further illustrated in *Figure 5* (12). Although the inclusion criteria and the definition of growth are

Table 2 Natural history of GGO based on more than 100 lesions

First author [year] (references)	Inclusion criteria			Patients	Lesions	Follow-up time (years)	With growth [n, %]
	Size	GGO proportion	Follow-up period				
Hiramatsu [2008] (37)	–	Any	≥3 months	125	125	2.9[a]	26[c] [21]
Matsuguma [2013] (38)	≤2 cm	>20%	–	171	174	2.4[a]	41[d] [24]
Chang [2013] (39)	–	100%	>2 years	89	122	4.9[b]	12[e] [10]
Lee [2013] (40)	–	Any	>2 years	114	175	3.8[b]	46[e] [26]
Kobayashi [2013] (12)	≤3 cm	≥50%	≥6 months	61	108	4.2[b]	29[e] [27]

a, mean; b, median; c, growth was defined as ≥2 mm increase in whole GGO size, ≥2 mm increase in the solid component, or emerging new solid part of any size; d, growth was defined as ≥2 mm increase in whole GGO size, ≥2 mm increase in the solid component, or emerging new solid part ≥2 mm; e, growth was defined as ≥2 mm increase in whole GGO size.

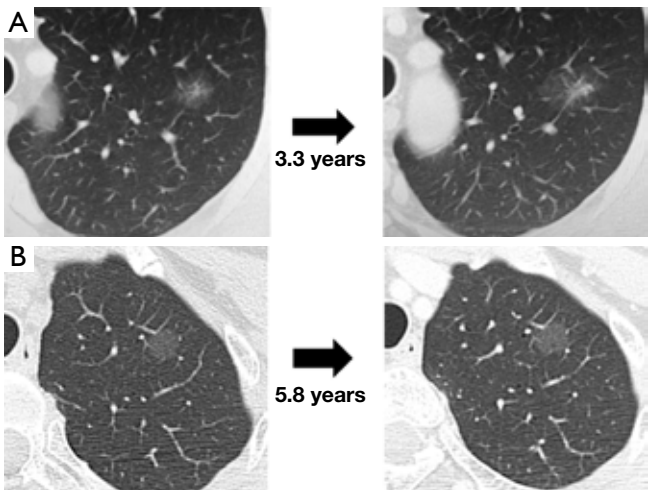

Figure 4 Computed tomography images of two representative pulmonary nodules with GGOs. A, A part-solid GGO lesion became larger, and its solid component increased after 3.3 years. B, A pure GGO lesion persisted without changing in size for 5.8 years.

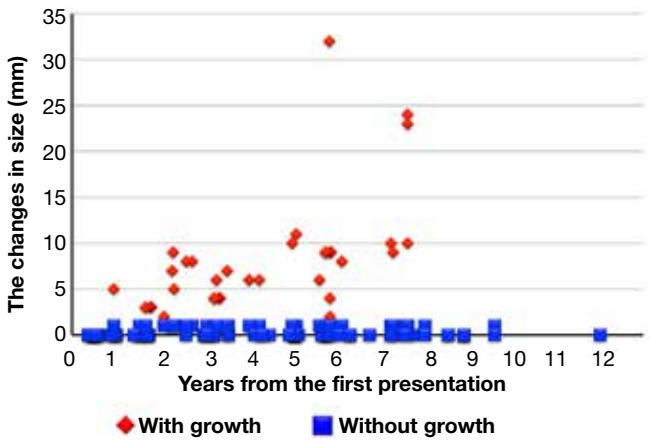

Figure 5 Changes in the sizes of the 108 evaluated lesions from the time of the first presentation to the last CT scan. Twenty-nine lesions (red) increased by 2 mm or more, whereas the remaining 79 lesions (blue) persisted without changing in size. Adapted with permission from Wolters Kluwer Health©. Kobayashi Y. *et al.* J Thorac Oncol 2013;8:309-14.

variable, 10% to 27% of GGOs gradually grow, whereas others persist without changes for years (12,37-40). It should be noted that according to the updated data from our study, even some part-solid GGOs remained unchanged for more than 3 years; these included 45 pure GGOs (size range, 4 to 16 mm) and 7 part-solid GGOs (size range, 7 to 12 mm). However, the solid component proportions of these 7 part-solid GGOs were only 1%~25%.

To discuss the difference between the natural history of pure GGOs and that of part-solid GGOs, we summarized them separately. Among the 5 reports mentioned above, 4 included the natural histories of pure GGOs, and these are summarized in *Figure 6* (12,38-40). Approximately 80% of pure GGOs remained unchanged, while others grew in size or progressed to become part-solid GGOs. In comparison, the natural histories of part-solid GGOs were available in 3 reports; these histories are summarized in *Figure 7* (12,38,40). Approximately 60% of the part-solid GGOs remained unchanged. These findings indicate that part-solid GGOs seem more likely to grow than pure GGOs are.

Volume-doubling time (VDT) of nodules with GGO

The VDT is useful for objectively evaluating GGO-predominant lesions' tendency to grow. Based on the two-dimensional calculation method, the mean VDTs of 19 pure GGOs and 19 part-solid GGOs were 813 days (±375) and 457 days (±260), respectively (41). Other studies reported

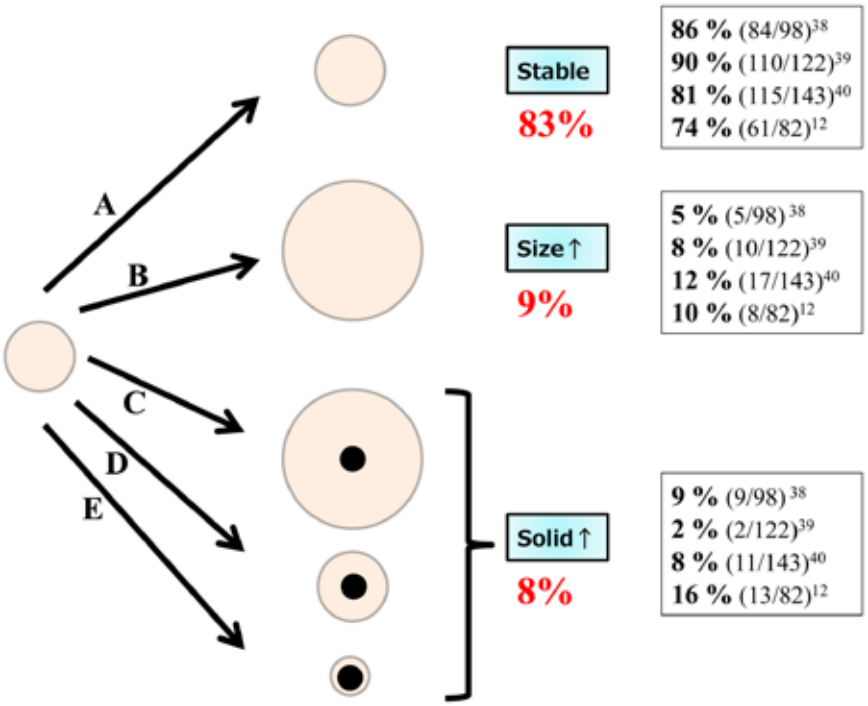

Figure 6 The natural history of pure GGOs. Five types of progression are suggested: A. no change; B. the size of the lesion increases, but there is no solid component; C. the size of the lesion increases, and a solid component appears; D. the solid component increases with no change in lesion size; and E. the size of the lesion decreases, and a solid component appears. The frequencies of each type are summarized. Approximately 80% of the pure GGOs remained unchanged.

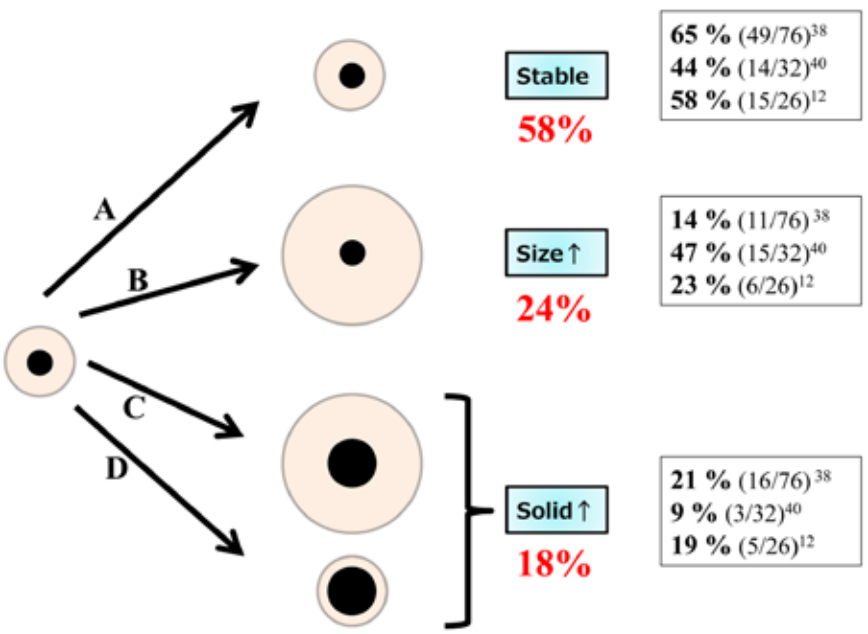

Figure 7 The natural history of part-solid GGOs. Four types of progression are suggested: A. no change; B. the size of the lesion increases, and the solid component remains unchanged; C. the size of the lesion and the solid component increases; D. the solid component increases, with no changes in the lesion size. The frequencies of each type are summarized. Approximately 60% of the part-solid GGOs remained unchanged.

similar results: the mean VDT of pure GGOs ranged from 769 to 880 days (39,40,42). In a recent study using computer-aided three-dimensional evaluation, the mean VDTs of 19 pure GGOs and 28 part-solid GGOs were 629 (±404) days and 277 (±156) days, respectively (43). Based on these data, the VDT of pure GGOs was consistently longer than that of part-solid GGOs.

How long should we follow up nodules with GGO?

It is unclear how long we should follow GGO-predominant lesions that do not meet the criteria for surgical intervention. We analyzed the time at which lesions with GGO began to grow. Among the 108 lesions that met the abovementioned criteria, 29 lesions grew at the median follow-up period of 4.2 years. All 29 of the lesions began to grow within 3 years from the time of the first observation; of these, 13 lesions grew within 1 year, 12 lesions grew within 1.1 to 2 years, and 4 lesions grew within 2.1 to 3 years (12). Therefore, we concluded that such lesions should be followed for at least 3 years to accurately evaluate the lesion growth.

We discuss the appropriate follow-up period based on the VDT of GGO-predominant lesions. We computationally simulated the size changes of pure GGO lesions using the VDT of 813 to 880 days. A 5-mm lesion would grow to 6.7 to 6.8 mm after 3 years of observation, whereas a 10-mm lesion would grow to 13.3 to 13.6 mm within the same period (12). Are these small changes in size (i.e., 1.7 to 1.8 mm and 3.3 to 3.6 mm) detectable on CT examinations? Measurement errors should be considered when we evaluate the increase in size. Kakinuma *et al.* reported that increase in diameter of >1.72 mm is necessary to identify true growth, considering interobserver measurement errors (44). Therefore, these calculated changes in size should be detectable with CT analysis, and the follow up period of 3 years seems to be reasonable.

It should be noted that the range of the VDTs stated above was wide in each study, and a few lesions actually began to grow after 3 years of observation (37-39). However, it is reasonable to regard the 3-year observation follow-up period as a benchmark for GGOs because the exceptional cases are in the minority.

Surgical procedure

When the GGO lesion in question is indicated for surgical resection, the extent of surgical resection presents another question. The standard treatment for operable non-small cell lung cancer is lobectomy with dissection of the ipsilateral hilar and mediastinal lymph nodes (45). Asamura *et al.* reported the prognosis of 545 patients who underwent lobectomy and lymph node dissection in the abovementioned multi-institutional prospective study (30) to predict pathological noninvasiveness. At the median follow-up period of 7.1 years, with the use of the cutoff value of an adenocarcinoma ≤3 cm with a C/T ratio ≤0.5, the 5-year overall survivals of radiologic noninvasive (121 patients) and invasive (424 patients) adenocarcinomas were 96.7% and 88.9%, respectively, and the difference was statistically significant (P<0.001). With the cutoff value of an adenocarcinoma ≤2 cm with a C/T ratio ≤0.25, the 5-year overall survivals of radiologic noninvasive (35 patients) and invasive (254 patients) adenocarcinomas were 97.1% and 92.4%, respectively, and the difference was not statistically significant (P=0.259) (46). These data showed that most of the patients with adenocarcinoma ≤3 cm with a GGO component >50% were cured by lobectomy.

Based on these favorable prognoses, limited surgical resection that preserves lung parenchyma might be indicated for patients with such GGO-predominant lesions. There have been many reports on recurrence-free survival after the limited resection of a GGO lesion. For example, 35 patients with pure GGOs ≤2 cm survived without recurrence after partial resection in 31 patients and segmentectomy in 4 patients (6). Similarly, 48 patients with lesions ≤2 cm with GGO proportions >50% survived without recurrence after partial resection in 33 patients and segmentectomy in 15 patients (47).

In contrast, local recurrence has also been reported. Nakao *et al.* reported that 4 out of 26 patients with GGO lesions ≤2 cm developed either cut-end recurrence or metachronous primary disease more than 5 years after the initial limited resection (48). In their study, a resection margin greater than 1 cm was ensured (48). Possible reasons for the cut-end recurrence are the difficulty of intraoperatively localizing the GGO and the vague GGO border. The preoperative CT-guided injection of agar near the target GGO lesion has been reported to be useful for making deeply located lesions palpable (49). Furthermore, intraoperative ultrasonography facilitated effective localization in a completely deflated lung and was useful for evaluating surgical margins (50). This method can be performed in complete video-assisted thoracic surgery.

Regardless of the favorable prognoses that were achieved by limited resection in the retrospective studies, prospective

clinical trials are necessary to establish the efficacy and safety of limited resection. There are two ongoing clinical studies in Japan to assess the efficacy of limited surgical resection for small lung cancer lesions. One study is a Phase III trial comparing lobectomy and segmentectomy for small radiologically invasive lung cancer, which is an adenocarcinoma ≤2 cm with a C/T ratio >0.25 (51). Another study is a Phase II trial of a wedge resection for small radiologically noninvasive lung cancer, which is an adenocarcinoma ≤2 cm with a C/T ratio ≤0.25 (52).

Conclusions

Surgery achieves favorable prognoses in patients with GGO-predominant lesions. However, the natural history of GGOs has been gradually clarified; some of them grow or increase their solid component, whereas others remain unchanged for years. Therefore, it remains unclear whether all GGO-predominant lesions should be surgically resected, and whether lesions without changes may not require resection. To distinguish GGOs with growth from those without growth, a 3-year observation period is a reasonable benchmark for follow-up. Future studies on the genetic differences between lesions with and without growth will help establish an appropriate management algorithm.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Computed tomography guided microcoil localization for pulmonary small nodules and ground-glass opacity prior to thoracoscopic resection

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Background: To evaluate the feasibility, safety and efficacy of computed tomography (CT)-guided microcoil localization for small pulmonary lesions prior to thoracoscopic resection.

Methods: We retrospectively reviewed the medical data of patients with pulmonary solid nodules and ground-glass opacity (GGO) who underwent CT-guided microcoil localization prior to thoracoscopic surgery. The microcoil was deployed with the proximal end of the microcoil coiling beyond the parietal pleura while the distal part anchoring in the lung parenchyma. After marking with microcoil, the pulmonary lesions were removed by thoracoscopic surgery.

Results: CT-guided microcoil placements were successful in all 98 lesions, including 14 solid nodules, 11 part-solid GGO, and 73 pure GGO. The mean distance from the lesions to the pleura surface was 11.1±6.6 mm. Eighty-four microcoils (85.7%) were successfully placed with the tails coiled beyond the parietal pleura. Seventeen patients (17.3%) had mild complications after the procedure of localization. Thirteen patients with asymptomatic pneumothorax, only one patient required further thoracentesis, four patients with pulmonary hematoma. Removal of the pulmonary lesions was successful in all patients. Sixty-six lesions (67.3%) were localized through the proximal end of the microcoil beyond the visceral pleura by visual inspection, 29 lesions were localized by palpation of the microcoil or the nodule, and 3 lesions had dislocation of the microcoil, resulting in a success rate of 96.9% for intraoperative localization.

Conclusions: CT-guided microcoil localization prior to thoracoscopic resection is a feasible, safe, and effective method for localization of pulmonary small nodules and GGO.

Keywords: Lung cancer; thoracoscopic; nodule; localization

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Introduction

Video-assisted thoracoscopic surgery (VATS) has become the main surgical intervention tool for diagnosis and treatment of small pulmonary nodules and ground-glass opacity (GGO). However, intraoperative localization of small pulmonary lesions tends to be difficult (1). Preoperative localization is very helpful for guiding resection through VATS, which mainly adopts computed tomography (CT)-guided percutaneous lung puncture technology by placing a medium in the lung for localization of intraoperative lesions (2). The selection of medium is the key for localization efficacy. In 1994, Asamura first

reported the use of a platinum microcoil, which is usually intended for embolization of selective vessel supply, for positioning small pulmonary nodules (3). Powell developed a better method by deploy the microcoil with the end coiled in the pleural space (4). We have performed preoperative microcoil localization since 2012 in our institution. And we adopted a way to deploy the microcoil somewhat different from Powell's method. In this study, we introduce our method and evaluate the feasibility, safety and efficacy of preoperative microcoil localization for small pulmonary lesions in our single institution.

Methods

Study subjects

Retrospectively reviewed the data of patients with small pulmonary solid nodules and GGO who underwent microcoil localization prior to thoracoscopic surgery from March 2013 to November 2014 in Peking University People's Hospital, Beijing, China. Preoperative localization using microcoil was conducted in lesions according to the following conditions: (I) solid nodules with a diameter ≤1 cm and distance to visceral pleura ≥0.5 cm; (II) GGO; (III) part-solid GGO, with a solid portion ≤1 cm and distance to the visceral pleura ≥1 cm. Of all the patients, patients who underwent preoperative localization by deploying the end of microcoil coiled outside lung parenchyma were included in this study. As standard of care, all patients signed informed consent form before preoperative localization. Our institutional review board approved the present retrospective study and waived the requirement for informed consent for collecting medical data from the related patients.

Microcoil localization

Patients underwent CT-guided percutaneous pneumocentesis for positioning within three days prior to surgery at our radiology department. Embolization Microcoil (Cook incoporated, Bloomington, IN 47404, USA) was selected as positioning markers, with a wire diameter of 0.18″ and a length of 7 cm. A percutaneous introducer kit (Argon Medical Devices Inc., Athens, TX75751, USA) with a 21 G puncture needle and a 45 cm ×0.18″ guide-wire) was used. Before puncturing, the desired length of the guide-wire was prepared with the whole length of the loading cannula connecting with the puncture needle. After local anesthesia with 2% lidocaine, the procedures are illustrated as follows: CT-guided percutaneous puncture was carried out using the puncture needle, during which the needle pathway avoided the lesions, and the tip was positioned in the normal lung parenchyma around the lesions. Successful puncture was confirmed by the CT scan and then the loading cannula of the microcoil was connected to the needle. Our method named "trailing" for deploy the microcoil was derived from Powell's method (4). However In our method, it was intended that the proximal end of the microcoil be left on the parietal pleura: at first the distance from the needle tip to beyond the parietal pleura was measured, and marked on the guide-wire (*Figure 1A*). The guide-wire was then inserted into the needle and advanced to the marked location, pushing the distal part of the microcoil into the lung parenchyma (*Figure 1B*). The guide-wire was fixed in place and the needle was withdrawn slowly with the proximal part of the microcoil remained in the needle tubing (*Figure 1C*). When the needle was withdrawn to the desired length on the guide-wire, the needle and guide-wire were withdrawn simultaneously and the proximal part of the microcoil was deployed. Scanning was conducted to confirm the position of the microcoil, where technical success referred to the proximal end of the microcoil coiling beyond the parietal pleura while the distal part anchoring in the lung parenchyma (*Figure 1D*). The presence of pneumothorax and hemorrhage was also assessed. Later patients were sent back to the ward. Patients who did not intend to undergo surgery on the same day underwent chest radiographs on the morning of the day for surgery or at the time of occurrence of symptoms.

Thoracoscopic surgery

Conventional thoracoscopic surgery was adopted. The patients were on ventilator with a double lumen endotracheal tube under general anesthesia. Later patients were placed in the lateral position with ipsilateral one-lung ventilation and two to three ports were made. The observation port was located at the midaxillary line of the 7^{th} or 8^{th} rib, the main operating port was located at the anterior axillary line of the 4^{th} or 5^{th} rib with a length of 3-4 cm, while the auxiliary incision was at the infrascapular line of the 7^{th} or 8^{th} rib. First, visual examination was done, and then positioning was determined by looking for the proximal end of the microcoil beyond the visceral pleura. If the marker was not found, palpation was conducted on the microcoils or lesions bypassing the main operating

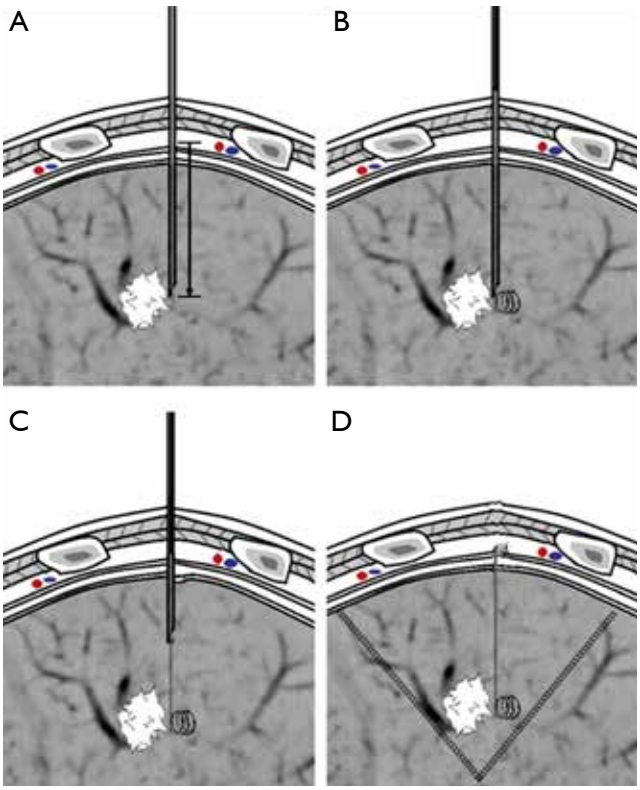

Figure 1 Schematic diagram of "trailing method" for deploying the microcoil. (A) The distance between needle tip and outside the parietal pleura was measured, and marked on the guide-wire; (B) the guide-wire was inserted into the needle and advanced to the marked location. The distal part of the microcoil was deployed and coiled in the lung parenchyma; (C) the guide-wire was held in place and the needle was withdrawn slowly. When the needle was withdrawn beyond the parietal, the needle and guide-wire were withdrawn simultaneously; (D) the microcoil was deployed with the proximal part coiling beyond the parietal pleura and the distal part anchoring in the lung parenchyma.

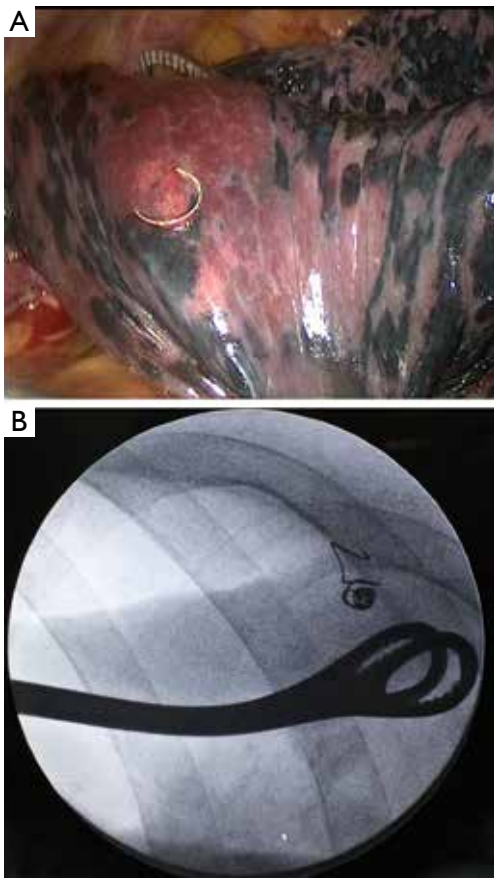

Figure 2 Wedge resection of a deep nodule under both thoracoscopic and fluoroscopic guidance. (A) The deep lesion was located by the microcoil on the visceral pleura surface under thoracosopic guidance; (B) the involved lung was grasped by a long oval forceps along the planned cutting line under fluoroscopic guidance, and the lesion was removed with endoscopic staplers beyond the forceps.

port. For cases with successful location by visual inspection or palpation of the microcoil or pulmonary lesions, pulmonary wedge resection or pulmonary segmental resection using endoscopic staplers was performed. For cases with unsuccessful palpation, fluoroscopy was utilized to find the microcoil and then pulmonary wedge resection or pulmonary segmental resection was performed and the integrity of the coil was confirmed. The incised specimens were subjected to intraoperative consultation with frozen section. For pulmonary malignancy, frozen section diagnosis was made not only including the initial diagnosis of lung cancer, but also a distinguishment between *in situ*, minimally invasive, and invasive adenocarcinoma. Based on the results of frozen section diagnosis, the operation could be ended for patients with benign lesions or noninvasive lung cancer. Patients with invasive lung cancer underwent thoracoscopic lobectomy and lymph node dissection or sampling. Patients with suspected invasive lung cancer were treated by lobectomy or sublobar resection and lymph node sampling following their willing in the informed consent preoperatively. If lesions were found in a deep location and enough margin distances were not achievable for sublobar resection under fluoroscopic guidance (*Figure 2*), thoracoscopic lobectomy was conducted and lesions were

Table 1 Patient and nodule characteristics

Characteristics	Value (%)
Patient characteristics	
Sex	
Male	27 (27.8)
Female	70 (72.2)
Age	55.0±9.9
Nodule size	9.6±5.0
Nodule type	
Solid	14 (14.3)
Part solid GGO	11 (11.2)
GGO	73 (74.5)
Nodule to pleural distance	11.1±6.6
<10 mm	41 (41.8)
10-20 mm	48 (49.0)
>20 mm	9 (9.2)
Nodule location	
Right upper lobe (RUL)	30 (30.6)
Right middle lobe (RML)	8 (8.2)
Right lower lobe (RLL)	16 (16.3)
Left upper lobe (LUL)	27 (27.6)
Left lower lobe (LLL)	17 (17.3)
Final pathology	
Begin	12 (12.2)
AAH	9 (9.2)
AIS	33 (33.7)
MIA	15 (15.3)
Invasive adenocarcinoma	27 (27.6)
Metastasis	2 (2.0)
Operation data	
Procedure	
Sublobar	57 (58.8)
Lobectomy after histological confirmation	30 (30.9)
Lobectomy	10 (10.3)
Margin status	
Negative	98 (100.0)
Positive	0
Intraoperative localization	
Visual inspection	66 (67.3)
Palpation of microcoil	14 (14.3)
Palpation of nodule	15 (15.3)
Dislocation of microcoil	3 (3.1)
Fluoroscopic guidance	6 (6.1)

GGO, ground-glass opacity; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma.

identified by palpation of the microcoil after the specimens were isolated

Data collection and statistical analysis

Clinical data, imaging data, surgical data, and postoperative pathological information, which included age, sex, location of lesion, characteristics of lesion, diameter, complications of localization, surgical strategies, pathology, intraoperative positioning methods, etc. were collected. Success rate was compared using the Chi-square analysis, with the significance level set at 0.05. Excel 2010 and SPSS18.0 software were used for analyzing the data.

Results

From March 2013 to November 2014, 1,219 patients with lung lesions underwent thoracoscopic surgery. A total of 97 patients (8.0%) were included in this study, of which 88 patients with solitary lesion, 8 patients with multiple nodules in same lobe and 1 patient with two separate nodules in ipsilateral different lobes. In total, 98 lesions were localized using the "trailing method" prior to thoracoscopic surgery. The demographic information is listed in *Table 1*. There were 14 solid nodules, 11 part-solid ground-glass nodules, and 73 pure ground-glass nodules, with a mean diameter of 9.6 mm (range, 4-26 mm). The mean distance from the lesions to the pleura surface was 11.1±6.6 mm.

CT-guided placements of microcoil were successful in all lesions. The technical success rate of deploying with the tail coiled beyond the parietal pleura was 85.7% (84/98) patients. Seventeen patients (17.3%) had mild complications detected by CT scan after the procedure of localization. Thirteen patients with asymptomatic pneumothorax, four patients with pulmonary hematoma. Of all the patients with mild complication, six (three asymptomatic pneumothorax, one symptomic pneumothorax, two pulmonary hematoma) underwent surgery on the next day of localization, and a chest X-ray was followed up before surgery. Only the patient with symptomic pneumothorax required further thoracentesis as lung collapse was greater than 50% and dyspnea was present.

All patients underwent thoracoscopic surgery; 42 patients (43.3%) underwent thoracoscopic surgery on the same day of localization, 49 patients (50%) on the next day, and 6 patients (6.1%) on the subsequent day. During the surgery, 66 lesions (67.3%) were localized through the proximal end of the microcoil beyond the visceral pleura by visual inspection, 29 lesions were localized by palpation of

the microcoil, and 3 lesions had dislocation of the microcoil, of which two were localized by palpation, and one was localized by the hematoma at puncture site, resulting in a success rate of 96.9% for intraoperative microcoil localization. All small pulmonary nodules and GGO were successfully resected, with a surgical success rate of 100%. Surgical procedures were all completed under thoracoscopy. Fifty-seven patients underwent sublobar resection, 31 for wedge resection, and 26 for segmentectomy. Nineteen patients underwent lobectomy when frozen section proved primary invasive malignancy, 11 patients underwent lobectomy respecting their choices when frozen section diagnosis deferred in assessment of invasion, and 10 patients who underwent lobectomy directly due to multiple lesions or deep location. Postoperative pathological examination revealed 33 cases of adenocarcinoma in situ (AIS), 15 cases of minimally invasive adenocarcinoma (MIA), 27 cases of invasive adenocarcinoma, 9 cases of atypical adenomatous hyperplasia (AAH), 2 cases of metastasis, and 12 cases of benign nodule. No recurrence was found with a median follow-up of 9 months.

Discussion

Advantages of microcoil localization

The microcoil used in this study was a platinum wire for embolization of vessel supply in vascular intervention surgery. There were several reasons for selecting the microcoil for localization: (I) it is commonly used, easy to acquire and inexpensive compared with other special hook wires, spiral wires, radionuclides, etc.; (II) it is a clinically proven material that can safely be sustained in the human body for a long time; (III) after implantation, it coils in the lung with a certain degree of hardness and it is radiopaque, which enables positioning by visual inspection, palpation, and fluoroscopy during surgery; (IV) the placement operation is not complicated and has good repeatability. Microcoil localization can also make up for the deficiencies of other materials (5-10): (I) compared with the commonly used hook wire, the microcoil can be retained in the patients' body and is not easily detached. Therefore, it is not necessary to perform surgery immediately after the localization; (II) compared with solvents such as iodine, complications caused by intravascular injection and solvent diffusion effects on localization need not be concerned. It is also suitable for patients with silicosis with deep pulmonary surface color and patients with chronic obstructive pulmonary disease; (III) compared with radionuclide, microcoil cannot be contamination through radiation, and does not require special equipment and personnel training. Therefore, it is believed that the microcoil is an ideal positioning material at present.

Principle of "trailing method"

In the first cases of microcoil localization in our institution, the entire microcoil was placed into the lung parenchyma, in which the microcoil was coiled as a helical configuration in the lung. Localization can be achieved using this method, but it is not intuitive and it requires intraoperative palpation or fluoroscopy. Powell *et al.* reported adjustment in the location of puncture needle tip using guidance through CT, and the microcoil was placed with the proximal end forming a compact helical configuration on the visceral pleural surface; hence localization could be achieved by visual inspection. The placement of the end of the microcoil in the chest wall was avoided in their study (4,11). In our method, it was intended that the proximal end of the microcoil be left on the parietal pleura. After the distal part of the microcoil was deployed and anchored in the lung parenchyma, the needle was withdrawn. The proximal end of the microcoil, which remained in the lumen of the needle, was stretched by the anchored part and presented a "comet tail" shape. Thus it was named as the "trailing method" (*Figure 3*). Since the guide-wire was introduced only beyond the parietal pleura, the proximal end of the microcoil was deployed beyond the parietal pleura as well. After performing one-lung ventilation and with lung collapse, the proximal end of the microcoil would hang on the chest wall or detach from the chest wall to the visceral pleural surface due to stretching by the pulmonary elastic recoil to facilitate intraoperative observation. Obviously the operation of "trailing method" is less complicated and can reduce the number of CT scans.

Success ratio of "trailing method"

Since this novel "trailing method" was used for microcoil localization, the success rate reached 70% for the first ten placements, and similar results were obtained for every subsequent ten placements (P=0.231, *Figure 4*), which indicated that this method is easy to perform. However, the probability of observing the proximal end of the microcoil at the visceral pleura decreased after intraoperative one-lung ventilation. This phenomenon may be related to the

following two reasons: first, the distal end of the microcoil detached from the lung and plunged to the pleura cavity, causing intraoperative positioning failure. There were three cases of dislocation in the present study; all were close to the visceral pleura. Seo *et al.* reported that the localization of the hook wire tip with sufficient depth from the pleural surface was crucial to the success of preoperative localization using hook wire (12). It was assumed that the cause of dislocation was to position the microcoil too close to the visceral pleura in this study. On the other hand, the main reason for failure to observe the proximal end of the microcoil was that the microcoil prematurely detached from the parietal pleura and retracted into the lung parenchyma due to its own elastic force. It was believed that the success rate can be improved by controlling the needling depth and length of the microcoil. In case of the former, it is not appropriate that the needle be close to the visceral pleura to avoid detaching from the lung and falling into the chest after delivery. However, too deep needling depth will increase risks of lung hematoma and bleeding (13). With regard to the length of the microcoil, a longer microcoil is preferred to ensure that the microcoil can coil into a larger ball and anchor in the lung to avoid causing dislocation, but it is also important to maintain sufficient length beyond

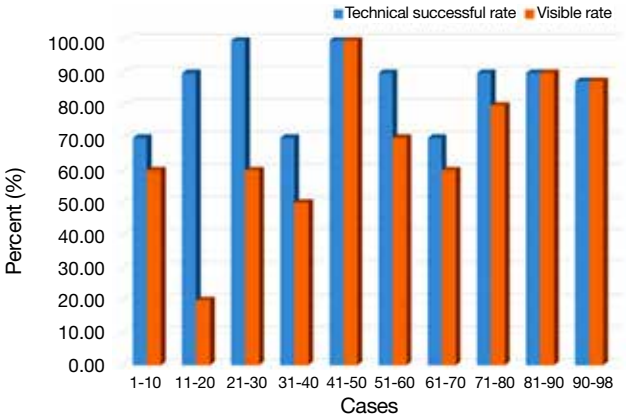

Figure 3 Technical success rate of the "trailing method" for every 10 lesions in a series of 86 lesions.

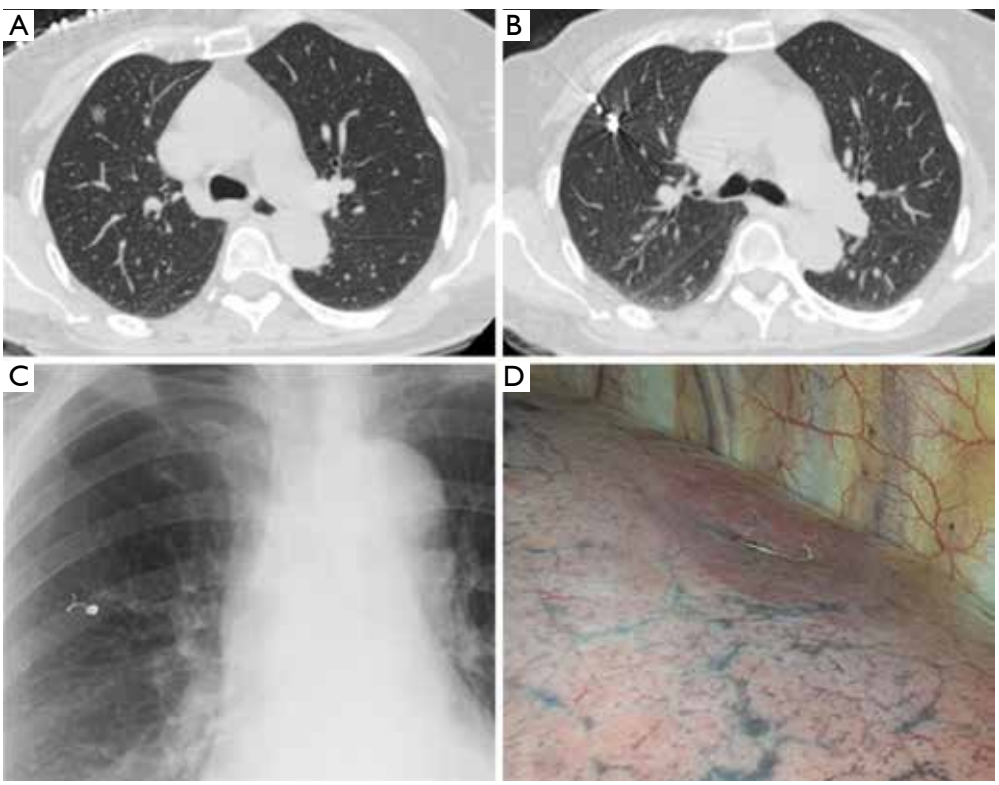

Figure 4 Microcoil localization using "trailing method". (A) A pure GGO in the RUL; (B) CT after localization using "trailing method"; (C) chest radiographs on the next day; (D) intraoperative observation revealed microcoil on the visceral pleura surface. CT, computed tomography; GGO, ground-glass opacity; RUL, right upper lobe.

the parietal pleura to prevent retraction of the microcoil in the lung. Referring to previous results, the depth of the needling tip should be between 1 and 2.5 cm (12,14) and the length of the microcoil should be longer than 6 cm when the "trailing method" was adopted. One aspect that needs to be emphasized is that the fixation of the puncture needle and guide-wire is the key for the "trailing method" since respiratory movement of the patients may cause changes in the needling depth in the process of delivery, resulting in placement failure.

Safety of microcoil localization

Microcoil localization was performed using CT-guided percutaneous puncture, which may present serious complications such as tension pneumothorax, bleeding, and even air embolism. Ichinose *et al.* performed percutaneous hook wire localization in 417 patients, and found that half of the patients presented with pneumothorax, of which 4.6% required pumping treatment, and the incidence of hemoptysis and hematoma was 10.3% while the incidence of air embolism was 0.24% (14). In this study, the complications of microcoil localization were also caused by puncture damage of lung tissues, of which pneumothorax usually occurred in lesions adjacent to the pleura or repeated puncture in multiple lesions, while hematoma was more common in lesions with deep location and longer traveling distance of needle, which was similar to previous results (13,14). Fewer complications were observed in our group compared with hook wire localization. This may be due to the smaller study size as well as early precaution and case selection using new technologies. It should be noted that though 52.9% (45/85) patients did not undergo surgery on the same day of positioning, more significant complications were not observed due to prolonged waiting time for surgery. It is believed that the structural characteristics of the microcoil might help in reducing the severity of complications. The thrombogenic coating of synthetic nylon fibers on the surface of the microcoil may promote blood coagulation of the surrounding lung tissues, block the needle pathway, and decrease the severity of pneumothorax and bleeding caused by the puncture needle damaging the lung tissues, which has been proven in animal experiments (15). However, the number of cases in the existing reports about microcoil localization was less (3,4,11,16) and there is lack of comparison with control groups. Further investigations are required to clarify its complications.

Indication of "trailing method"

In this study, the indication of preoperative localization was made based on the experiences of the thoracic surgeons in charge. During thoracoscopic exploration, 15/98 (15.3%) nodules was identified as palpable by the surgeons in charge, with 3/14 (21.4%) solid nodules, 1/11 (9.1%) part-solid ground-glass nodules, and 8 (12.0%) pure ground-glass nodules. Thus the indication of preoperative localization was considered reasonable though the detectability of solid nodules was better in the study. However, it should be reminded that the "trailing method" is not applicable for all lesions requiring localization. Generally speaking, lesions at deep location are usually removed by direct lobectomy, in which the microcoil will mark the lesion site to facilitate localization of the lesion in the resected specimen. In this circumstance, a visible tail of the microcoil is still helpful for quicker location in the resected specimen but it should be reminded hematoma is more common with greater needle insertion distance. If sublobar resection is to attempt for these deep lesions, a visible tail of the microcoil will facilitate defining both the location and the resection range of the nodules (*Figure 2*). The convenience of the "trailing method" is exceptional. However, the microcoil placed in the lung parenchyma has to be removed completely. The different routes for CT-guided percutaneous puncture and the endoscopic stapler placement may cause trouble for removing the microcoil placed by the "trailing method" in sublobar resection. In this study, lesions close to the scapula, armpit, and spine were found to be not suitable for the "trailing method". In other words, lesions in these positions are proposed as a relative contraindication of the "trailing method" if sublobar resection is planned.

Conclusions

In summary, CT-guided microcoil localization by "trailing method" prior to thoracoscopic resection is a feasible, safe, and effective method for localization of pulmonary small nodules and GGO and warrants further investigation.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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The imaging of small pulmonary nodules

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Abstract: Lung cancer is the leading cause of cancer death worldwide. The major goal in lung cancer research is the improvement of long-term survival. Pulmonary nodules have high clinical importance, they may not only prove to be an early manifestation of lung cancer, but decide to choose the right therapy. This review will introduce the development and current situation of several imaging examination methods: computed tomography (CT), positron emission tomography/computed tomography (PET/CT), endobronchial ultrasound (EBUS).

Keywords: Small lung nodule; computed tomography (CT); positron emission tomography (PET); endobronchial ultrasound (EBUS)

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Lung cancer is the leading cause of cancer death worldwide. Close to 70% of patients with lung cancer present with locally advanced or metastatic disease at the time of diagnosis (1). Screening of early lung cancer has been a continuing issue over the last 40 years.

Small lung nodule is a common problem in pulmonary practice. The definition of a classical solitary pulmonary nodule is a single, spherical, well-circumscribed, radiographic opacity less than or equal to 30 mm in diameter that is completely surrounded by aerated lung and is not associated with atelectasis, hilar enlargement, or pleural effusion (2). According to the density at thin-section computed tomography (CT), it is divided into nonsolid, ground-glass opacity (GGO), solid opacity (3). Possible causes of pulmonary nodules include many benign diseases, but the primary concern is bronchogenic carcinoma. Large tumor size and advanced stage are associated with worse prognosis. Rapidly identifying could not only avoid unnecessary surgery in patients with benign disease, but resect malignant lesions in a cost-effective manner. New developments in radiographic techniques as well as endobronchial ultrasound (EBUS) techniques have stimulated an increased interest in lung cancer screening. This review introduces the development of several imaging examination methods.

CT

In the 1970s, CT was invented by Hounsfield (4) and then applied to clinical. In 1989, spiral CT came out, since that it is playing a significant impact on the diagnosis of lung cancer. In 1990s, radiologists tried to diagnose the lung cancer based on clinical feature and CT-detected symptoms, and it had been recognized that there are some symptoms influencing the probability of cancer in a pulmonary nodule (5), including calcification (6),

size, change in size (7), number (8), density and so on. Short-term follow-up of pulmonary nodules with repeat volume measurements is believed to be the most reliable non-invasive method to distinguish between malignant and benign lesions (9). If a nodule doubles in volume in 1 month, its growth rate is uncharacteristic of lung cancer, a nodule grows at a rate consistent with cancer that doubles around 30 to 360 days (5).

Faced with a small pulmonary nodule, the radiologists must first assess the likelihood of lung cancer utilizing the parameters of age, nodule size, smoking history, spirometric findings, occupational history, the circumstances of the CT (baseline screen, interval 1-year screen, or study performed for other reasons), the number of nodules, the presence of radiographic or clinical signs of inflammatory lung disease, and the density of the nodule. According to the rule, if lung cancer is highly suspect, biopsy should be undertaken. If the nodule is judged to have an intermediate likelihood of being lung cancer, observation with a repeat CT in 6 to 12 weeks should be suggested. If resolution of the nodule occurs, no further evaluation is warranted. If a nodule fails to change over a 2-year period on CT, it is most likely benign; if it grows, biopsy should then be done. However, this necessary follow-up period is uncertain, and it may result in a delayed diagnosis of malignancy and consequently in delayed treatment. Besides, the accuracy of diagnosis by CT is not satisfied in 1990s, there are limitations. Many factors must be considered simultaneously. The images of the whole thorax is impractical which requires multiple breath-hold sets of contiguous spiral scans to cover the thorax completely with single-detector row CT (10). Respiratory motion is known to cause artifacts, which decrease tumor detectability, and alter quantification of localization in medical imaging (11-13). The radiologists' variable experience and perception capacity also greatly influence the accuracy of detection (14).

In 2000s, multi-detector row CT was used in screening programs, a CT exam can scan the entire thorax to acquire thin-section images in less than 10 seconds (15). Depending on the screening, the radiologists can get multiple spiral data during a single CT screening that helps them to generate clear CT images of different section thickness, even very small lung nodules. Computer-aided detection (CAD) methods to be applied to CT examinations are also formed to support radiologists to the large image data. Various CAD systems in chest radiography have been reported (16-18) and tested for the detection of lung nodules. CAD is designed to be used as a second reader; the diagnostic outcome is determined by both CAD analysis and the radiologists' diagnostic judgment. For example, De Boo *et al*. (14) conducted an observer study, they selected patients with CT and CXR within 6 weeks, and six readers of varying experience individually evaluated the CXR without or with CAD, then they calculated the sensitivity per lesion, figure of merit (FOM), and mean false positive per image (mFP). At last, they found the sensitivity increased for inexperienced readers (39% *vs*. 45%, P <0.05) with CAD and remained unchanged for experienced readers (50% *vs*. 51%). The mFP did not significantly increased for both inexperienced and experienced readers (0.27 *vs*. 0.34 and 0.16 *vs*. 0.21). All readers together dismissed 33% of true-positive CAD candidates. False-positive candidates by CAD provoked 40% of all false-positive marks made by the readers. This study showed that CAD could improve the sensitivity of inexperienced readers for the detection of small nodules and the diagnostic accuracy.

With the development of CAD, it come that CAD should be used as a first reader to reduce the radiologists' workload and reading time, and radiologists only inspect locations flagged suspicious by CAD, accept or reject the CAD marks. To fully utilize CAD as a first reader in lung CT screening, it is necessary that CAD reaches a high sensitivity for all screening nodules. In the past decade, efforts have been made to design generic CAD systems that detect all types of nodules. However, the published CAD systems still often missed important subgroups of suspicious nodules. For nodules larger than 5 mm, some kind of CAD systems achieved an average detection disappointing sensitivity. Although some modified CAD system could reach a high sensitivity of large nodules and the authors conclude that the proposed dedicated CAD system for large pulmonary nodules can identify the vast majority of highly suspicious lesions in thoracic CT scans with a small number of false positives (19), it still need more research.

As the developing of CT and the researches on pulmonary nodules, the details to describe pulmonary nodules are accurate and the existed guidelines on management of pulmonary nodules are changing. In 2015, the British Thoracic Society guideline based on a comprehensive and systematic review of the literature on pulmonary nodules published, which divided the persons into different group according to the size of the tumor and the rate of growth. People with nodule <5 mm diameter (or <80 mm^3) can be discharged. If the nodule is between 5 and 6 mm, it suggested people should have a CT scan 1 year later. If the nodule is >5 mm diameter (or ≥80 mm^3),

it suggested people should had a CT scan 3 months later. By evaluating the examination of the volume doubling time (VDT), doctors can made the proper management for the patients. This guideline showed the two malignancy prediction calculators to better characterize the risk of malignancy. The recommendations were a nodule size threshold for follow-up (≥5 mm or ≥80 mm^3) and a reduction of the follow-up period to 1 year for solid pulmonary nodules, which reduce the number of follow-up CT and improve cost-effectiveness and pressure on imaging services (20).

The maximum intensity projection (MIP) images are helpful for the diagnosis of small pulmonary nodules. It's invented by Jerold Wallis, MD, in1988. MIP is a volume rendering method for 3D data and is used for the detection of lung nodules in lung cancer screening programs which utilize CT scans, which enhances the 3D nature of these nodules, making them stand out from pulmonary bronchi and vasculature. A research about MIP reconstructions showed it remains a valuable adjunct to the interpretation of chest CT for increasing sensitivity and has the advantage of significantly lower false-positive rates (21).

CT-guided percutaneous transthoracic needle biopsy (PTNB) is also established and matured. PTNB is advantageous in diagnosing peripheral lung lesions for high accuracy and safety (22), and complication rates are acceptable (23). Getting the tissue from the small lung nodule by PTNB is minimally invasive way to detect the mutation, which is not only useful for the diagnosis, but for the making therapeutic regimen.

Positron emission tomography/computed tomography (PET/CT)

Positron emission tomography (PET) is the most important advance in lung cancer imaging since the applying of CT scanning. When 18F-FDG is injected intravenously, it is taken up by tumor cells at a higher rate than in normal cells. Lung cancer cells have a particularly high avidity for FDG. The emergence of combined PET/CT imaging has greatly aided the investigation of lung cancer. In a retrospective study on identification of characteristics of solitary pulmonary nodule, the sensitivities of CT, PET and PET/CT were 93%, 69% and 97% while specifies were 31%, 85% and 85% (24). PET/CT has been shown to be invaluable for detecting distant metastasis, particularly in patients already known to have a primary tumor. In patients with confirmed non-small cell lung cancer (NSCLC), PET/CT has also repeatedly been shown to be more sensitive and specific than conventional noninvasive imaging methods for staging of the mediastinum (25). For these reasons, PET/CT has become widely used for staging of NSCLC is performed using the tumor, node, metastasis (TNM) classification system. The TNM staging system is presently the standard tool for staging lung cancer patients. The system is based on a combination of three basic aspects: the location and extent of the primary tumor (T); the presence or absence of changes in intrapulmonary, hilar, or mediastinal lymph nodes (N); and the presence or absence of other pulmonary nodules, pleural effusion, or extrathoracic (distant) metastases (M). The combination of the T, N and M scores is then used to place a given lesion in one of four disease stages (I–IV), stratifying individuals by prognosis and therapeutic prospects. PET has been used to assist in determining the presence of malignancy in SPNs, although, even in lesions over 1 cm in size, it has become clear that PET cannot be considered conclusive. High levels of FDG uptake correlate strongly with malignancy, as well as with prognosis in patients with known NSCLC (26).

It is currently estimated that approximately 75% of all NSCLC patients could benefit from radiotherapy at some point during their treatment (27,28). Preliminary evidence suggests that FDG-PET may has value in the planning of radical radiotherapy for NSCLC by ensuring that all gross primary tumor (29). Inadequate imaging with CT will limit the value of radiotherapy because of failure to include all gross tumors in the radiotherapy target volume, which will lead to inadequate dose of radiation. PET scans may be useful for assessing response to nonsurgical therapy for NSCLC by imaging changes in FDG uptake in tumor volume (30).

Although PET/CT has proven to be a particularly promising modality in NSCLC staging, several pitfalls must be taken into account when interpreting PET/CT findings. Neither usually specific nor sensitive is the limitations of PET, particularly for small pulmonary nodules, because low-grade malignant tumor such as bronchiole-alveolar carcinoma and carcinoid are frequently negative for FDG-PET due to their low glucose metabolism, while active infection, inflammation, or pulmonary infarction, sometimes showed positive due to their high glucose metabolism (31). Besides, prior study (32) showed that the malignant nodules less than 1 cm were hard to image. The spatial resolution of current generation of PET scanners is 7–8 mm, which can hardly image pulmonary nodules <1 cm.

EBUS

CT for evaluation of primary tumors and metastases was effective; however, the reliability in predicting metastatic involvement of mediastinal lymph nodes an airway infiltration was disappointing. Besides, it is difficult to differentiate two adjacent structures of soft tissue that there is no difference in the density of water (33). As different from CT, ultrasound imaging is based on signals generated by ultrasonic waves reflected from different anatomic layers, and it depends on the density of the tissues passed and on the energy of ultrasonic wave. Transthoracic ultrasound cannot image of the mediastinal structures because of the limited acoustic window resulting from the reflection of the ultrasonic wave by air contained in the lung tissue, so study was focused on developing devices for endoluminal applications. In 1990, Becker developed a flexible catheter with an ultrasound probe for application inside the central airways which provided a 360-degree view of the parabronchial and paratracheal structure (34). The endobronchial application of ultrasound for the diagnosis of lung cancer was first described in 1992 (35). Since then, major technological advances have occurred and much published research was reported on the indication and diagnostic accuracy of EBUS. Nowadays, EBUS has emerged as a highly effective and minimally invasive technique for sampling peribronchial, mediastinal, and lung masses for pathologic examination.

EBUS plays a role in the staging of NSCLC and the diagnostic evaluation of endobronchial lesions, peripheral pulmonary nodules (PPNs), and mediastinal abnormalities. Chavez *et al.* (36) conducted a retrospective trial about the diagnostic performance of transbronchial biopsy (TBB) with EBUS-GS, they collected 212 patients with PPNs (≤30 mm), and found that the overall diagnostic accuracy of EBUS for PPNs and central parenchymal nodules is about 71% and 77%, which can be maximized for PPNs that are away from the pleura and when the EBUS probe can be placed within the lesion. Radial-endobronchial ultrasound (r-EBUS) is used to identify peripheral pulmonary lesions and sampling sites that provide a 360° radial image of the surrounding structures. Herth and coworkers (37) demonstrated that r-EBUS-guided transbronchial lung biopsy had a diagnostic yield of 80%. These researches showed r-EBUS is an acceptable diagnostic method for small pulmonary nodules. The 2013 ACCP guidelines on lung cancer diagnosis recommend radial EBUS when the appropriate instruments and a skilled operator are available (38).

Mediastinal lymph node staging is divided into noninvasive and invasive staging. Noninvasive techniques include CT, magnetic resonance imaging (MRI), PET, and PET/CT. The sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis is 51% (95% CI, 47%~54%) and 85% (95% CI, 84%~88%), the sensitivity and specificity of PET scanning for identifying mediastinal metastasis is 74% (95% CI, 69%~79%) and 85% (95% CI, 82%~88%), respectively (39). These data demonstrate that while PET is more accurate than CT, the technology is still fallible. Some studies (40-42) using EBUS for mediastinal staging showed strong sensitivity and specificity. In 2006, Herth and colleagues (42) evaluated EBUS-TBNA in patients with lung cancer and a radiographically normal mediastinum; this study showed an unexpected detection rate of mediastinal metastases of 17% in 119 lymph nodes 5 to 10 mm in size. Endoscopic ultrasound-fine needle aspiration (EUS-FNA) and EBUS-TBNA are sometimes combined because EUS has better access to the posterior and inferior mediastinum, and EBUS to the anterior and superior mediastinal lymph nodes. Wallace and coworkers (43) compared the diagnostic accuracy of transbronchial needle aspiration, EBUS-TBNA, EUS-FNA, and their combinations. They reported a sensitivity of 93% (95% CI, 81%~99%), and a negative predicted value of 97% (95% CI, 91%~99%) for the combination of EUS-FNA and EBUS-TBNA in a population with a prevalence of mediastinal metastases of 30%. In addition, they reported that the combination of EUS-FNA and EBUS-TBNA was better than either alone, even when evaluating scenarios that favored one technology over the other. Both technologies far outperformed blind TBNA in assessing mediastinal lymph nodes.

Virtual bronchoscopic navigation (VBN) is a method to guide a bronchoscope to a peripheral lesion under direct vision using virtual bronchoscopic images of the bronchial route. Virtual images can be prepared using commercial general-purpose image preparation software. Electromagnetic navigation (EMN) is a relatively new navigation method that utilizes electromagnetism. An electromagnetic field is prepared around the patient's chest, and biopsy instruments are guided to a pulmonary lesion based on the positional information of the electromagnetic micro-center and CT information acquired beforehand (44). Ultrathin bronchoscopy with a working channel applicable for biopsy has recently been used not only for bronchoscopy in children but also in diagnosing peripheral pulmonary lesions in adults (45). Each technique has advantages and disadvantages, and it is necessary to understand these and investigate

appropriate combinations corresponding to individual cases.

In conclusion, there have been great advances in image processing allowing for both characterization and detection of small pulmonary nodules, but the early diagnosis of lung cancer is still very hard. Crucial breakthrough is still needed. Mixing with several detection methods may lead to technological improvement. The new idea to diagnose and evaluate lung cancer is also looking forward.

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Footnote

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Risk assessment in relation to the detection of small pulmonary nodules

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Abstract: The National Lung Cancer Screening trial (NLST) demonstrated that individuals assigned to the LDCT screening arm had a 20% lower mortality than those who were assigned to the conventional chest radiography. The NLST was thoroughly analyzed by the US Preventive Task Force on CT Screening and they recommended that lung cancer screening should be implemented. A number of other countries have also recommended implementation, whilst others are awaiting the outcome of the NELSON Trial. However, recommendations for the management of CT screen detected nodules have only recently had any clarity. The management of CT detected nodules in the NLST was based on the identification and reporting of 4 mm diameter nodules found on the CT screens but there was no NLST radiology protocol in place for the management of nodules. The use of volumetric analysis is not routinely used in the USA and there is still a reliance on utilising the CT nodule diameter as the management parameter. The first pulmonary risk model was developed by the Canadians, utilising data sets from the Pan-Canadian Early detection of Lung cancer (PanCan) and validated in the chemoprevention trial dataset at the British Columbian Agency. This Canadian model, known as the Brock Model, is currently available and has been integrated into the British Thoracic Society guidelines on the management of pulmonary nodules. The American College of Radiology setup a Lung Cancer Screening Committee subgroup on Lung-RADS, to standardize lung cancer screening CT reporting and provide management recommendations. However, it has been recommended that the Lung-RADS system should be revised as the system as it has never been studied in a prospective fashion. The NELSON trial introduced a third screening test, the "indeterminate" screening test result, this was done with the aim to reduce the false-positives CT screening results and also utilized by the UKLS trial successfully. On comparing the radiological CT screen volumetric and diameter based protocols in the NELSON trial, the sensitivity and negative predictive value appeared to be comparable, however a higher specificity and positive predictive value was found for the volume-based protocols, thus confirming the advantage of utilising the volumetric approach over diameter The British Thoracic Society (BTS) has undertaken an in-depth piece of work developing guidelines on the management of pulmonary nodules, utilising the wealth of data published by the NELSON team and support the use of volumetric analysis for the management of pulmonary nodules.

Keywords: Lung cancer; risk prediction; pulmonary nodules; management

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The use of low dose CT (LDCT) for early lung cancer detection in high risk individuals has progressed from the first publication by Henschke *et al*. (1), through to the National Lung Cancer Screening trial (NLST) in 2011 (2), to the current data from the NELSON trial on the management of small pulmonary nodules. The NLST demonstrated that individuals assigned to the LDCT screening arm had a 20% lower mortality than those who were assigned to the conventional chest radiography. The current status of lung cancer screening trials has been extensively reviewed over the past three years, demonstrating the enormous strides in the management of lung cancer screening (3-6).

Clearly the stage has been set in the USA for the implementation of lung cancer screening based on the NLST trial publication and also on the recommendation from the US Preventive Services Task Forces (USPSTF) (7) on lung cancer screening, resulting in the agreed funding from March 2016 by the Center for Medicare (8) and Medicaid (CMS). The USPSTF recommended annual screening for lung cancer in the 55–80 age group who have a 30-pack-year smoking history and were either current smokers or have quit within the last 15 years. The independent review set up by the USPSTF modelled screening policies and investigated the long-term harms and benefits of lung cancer screening. The USPSTF have indicated that the parameters for selection should be review in time together with the management of these patients.

We currently await the publication of the NELSON trial, which will provide valuable information on mortality and cost effectiveness, from the only fully powered European trial. However, all of the main CT screening trials have consistently demonstrated that early Stage disease is one of the core findings, with 81% from International Early Lung Cancer Detection Program (IELCAP), 63% from NLST, 73% from NELSON and 67% from the (United Kingdom Lung Screening (UKLS) trial (*Table 1*), compared to the expected ~15%. It also note that a number of pilot European CT screening trials have provided an in-depth insight into the management of CT detected nodules.

The management of CT detected nodules in the NLST was based on the identification and reporting of 4 mm diameter nodules found on the CT screens but there was no NLST radiology protocol in place for the management of nodules. Clearly, the early work undertaken by IELCAP initiated the debate on utilising volumetric measurements for the management of small CT detected nodules. This work has been further developed by the NELSON group and latterly validated by the UKLS trial.

The use of volumetric analysis is not routinely used in the USA and there is still a reliance on utilising the CT nodule diameter as the management parameter. The Canadian Pulmonary Risk model was developed utilising datasets from the Pan-Canadian Early detection of Lung cancer (PanCan) and validated in the chemoprevention trial dataset at the British Columbian Agency (BCCA) (9).

Characterisation of nodules is well described within the PanCan risk model publication included a range of

Table 1 Early stage cancers identified in lung cancer RCT trials

Trial	Participants in screening arm	Screening rounds	No. published CT detected lung cancers	Stage IA & IB lung cancers (%)
NLST	26,722	3	649	400 (61.6)
NELSON	7,915	4	209	148 (70.8)
DLST	2,052	5	69	47 (68.1)
ITALUNG	1,613	4	22	11 (50.0)
DANTE	1,276	4	58	41 (70.7)
MILD	1,190	10	20	18 (62.1)
	1,186	5	22	14 (70.0)
LUISI	2,029	4	22	18 (81.8)
UKLS	1,994	1	42	28 (67.8)
Total	54,977	1–10	1,120	725 (64.0)

NLST, National Lung Cancer Screening trial.

imaging parameters including speculation, which was found to be a major predictor in the PanCan dataset, however, was not confirmed within the BCCA, as this data was not collected. The authors went on to develop parsimonious and full models with and without nodule spiculation. The model's discrimination i.e. a measure of how well such model can separate diseased from non-diseased individuals is most often measured using the area under the receiver characteristic (ROC) curve or c-statistic (10). Halligan *et al.* has identified problems with ROC and argued that it depends on the method used for curve fitting and does not account for prevalence or different misclassification costs arising from false-negative and false-positive diagnoses (11). Other methods and metrics of the performance of prediction models, such as the net benefit, have been proposed based on the change in sensitivity and specificity at clinical relevant thresholds (12). A major strength of this model is that it does not solely rely on ROC because comparison of the models with and without spiculation showed no significant differences in AUC but the net re-classification between the two models did suggest that spiculation could improve prediction. Net benefit incorporates estimates of prevalence and misclassification costs, and it is clinically interpretable since it reflects changes in correct and incorrect diagnoses when a new diagnostic test is introduced (11,12). The take home message was that if a threshold of at least 5% risk of lung cancer is used in the parsimonious model including spiculation, the sensitivity, specificity, positive predicative value and negative predicative value were: 71.4%, 95.5%, 18.4% and 99.6%. Thus, the model developed by McWilliams *et al.* can be used to accurately estimate the probability that lung nodules detected on baseline screening with low-dose CT scans are malignant. This model showed good accuracy for determining likelihood of malignancy in nodules detected on CT scans (13). However, in patients undergoing (fluorodeoxyglucose positron emission tomography-computed tomography) FDG PET-CT for nodule evaluation, the highest accuracy was seen in the Herder and co-workers risk model (14).

Lung CT screening Reporting and Data System (Lung-$RADS_{ver1}$) was published in 2014 (15). The American College of Radiology setup a Lung Cancer Screening Committee subgroup on Lung-RADS, in order to have a quality assurance tool to standardize lung cancer screening CT reporting and also provide management recommendations. The rationale behind this initiative is the hope that it would assist in lung cancer screening CT nodule scan interpretations. However, when Lung-RADS performance was compared to the NLST screening trial data, certain issues arose, even though NLST summary data was used to construct the Lung-RADS scores (16). The comparative performance indicated that Lung-RADS substantially reduced the false positive result rate and the sensitivity level decreased. Recently it has been recommended by Mehta *et al.* that the Lung-RADS system needs to be revised and faulted the system on the basis that it has never been studied in a prospective study.

Li *et al.* have recently analysed the size and growth of pulmonary nodules, as a consequence of 'rounding up' methodology used in Lung-RADS (17). The example given is if a nodule with an average diameter of 5.5 mm is reported as 6 mm diameter since 6 mm diameter is the current threshold for a positive result, further workup would be recommended for this nodule. Thus, rounding up to the nearest whole number increases the frequency of positive results which require further work-up before the next scheduled screening round. The authors also indicated another possible confusion, as to whether the length or the width is rounded up, which is not indicated in the Lung-RADS criteria. The authors concluded that with the move towards the utilisation of computer aided techniques, rounding up will be used less often, furthermore, the trend towards volumetric assessment of nodules, will result in a much more precise methodology.

The NELSON trial introduced a third screening test, the indeterminate screening test result, this was done with the aim to reduce the false-positives CT screening results (18). The importance of this decision is seen in the low percentage of false positives found in the NELSON trial. Especially, when one looks at the impact of the false positive screening test, with potential unnecessary work-up and invasive procedures and the possibility of overtreatment and the extra anxiety for the patients.

In the UKLS (19), a very clear definition was made for false positive tests as those requiring further diagnostic investigation more immediately than a repeat annual screen, but who subsequently did not have lung cancer. The proportion of false positive tests was provided in two ways, which allows an appreciation, in a patient-centered approach, of the variable impact on the subject in a trial or the patient in a programme. A "false positive" that mandates referral to the lung cancer multidisciplinary team (MDT) clinic will usually be associated with significant psychological distress, and additional invasive investigations with, in some cases, definitive treatment. An individual with a false positive as defined above is more likely to suffer harm

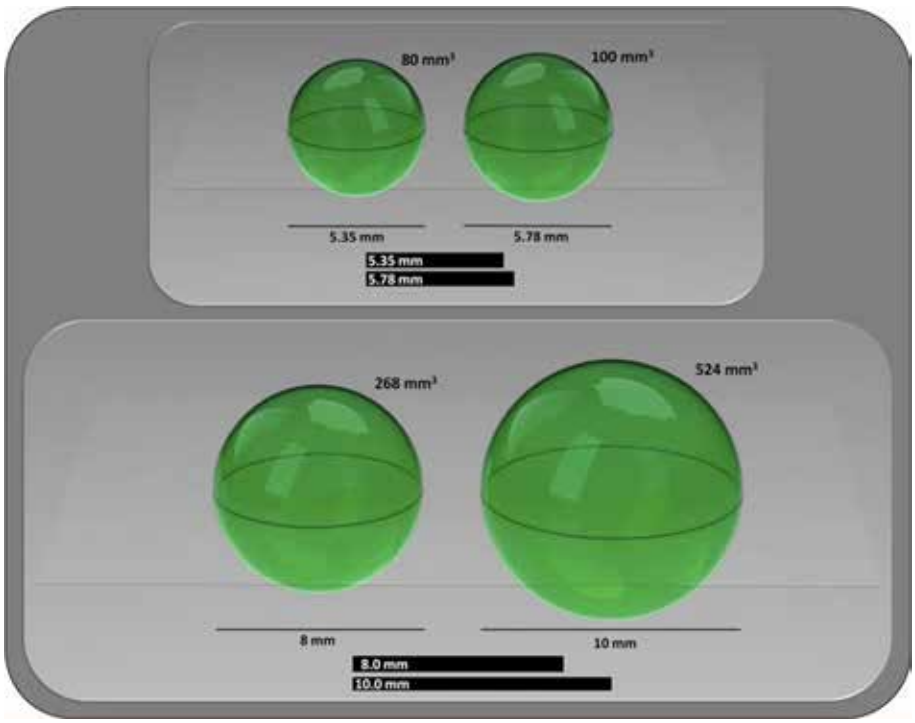

Figure 1 Comparison of the diameter and volume of CT screen detected nodules. (A) A volume growth of 26%, defined as growth by NELSON criteria, is hardly appreciable by diameter measurement (8% diameter increase which is NO growth by current criteria); (B) a 25% diameter increase i.e., threshold for the current growth definition reflects almost a doubling in volume (95%). It reflects the insensitivity for growth of diameter measurement. Reproduce from reference (3).

than one defined in a different way; that is, those subjects who are recalled solely for further CT imaging to clarify the nature of a nodule. The latter is best termed "Interval Imaging Rate" and may, in screening programmes, merely mean continuing in the programme rather than referral to the MDT. For this reason, all category three lesions in the UKLS trial without cancer (or called indeterminate nodules) were reported separately as false positives warranting interval imaging (19).

In the UKLS, the false positive rate was 3.6% whilst the interval imaging rate was 23.2% amongst participants referred to MDT clinic. The NELSON trial reported their false positive rate in 2013 as 3.6% (20). Both the UKLS and the NELSON utilised the indeterminate screening result whenever the participant received a repeat test within a period of three months, which was analysed by utilising volumetric analysis. A 25% increase in volume was considered as 'nodule growth' and the patient was then referred to the MDT for conventional clinical work-up. The advantage of utilising volumetric analysis is diagrammatically demonstrated in *Figure 1*. On comparing the radiological CT screen volumetric and diameter based protocols in the NELSON trial, the sensitivity and negative predictive value appeared to be comparable, however a higher specificity and positive predictive value was found for the volume-based protocols (21) thus confirming the advantage of utilising the volumetric approach over diameter.

The data discussed so far in this article relates to baseline data with nodule follow-up, however, the trial data which is relevant for routine screening are on new and incidental nodules comes from the extensive work undertaken by the NELSON team. NELSON calculated the risk of developing lung cancer based on the volume, volume based diameter in a large dataset of screened participants found to have non-calcified nodules and developed a probability table (*Figure 2*). It's of note that the probability was not significantly different between the NELSON participants with nodules <100 mm^3 compared to those with no CT detected nodules in the trial (0.6% *vs*. 0.4%). However, individuals with 100–300 mm^3 nodal volume had a higher probability of developing lung cancer (2.4%) and were considered indeterminate with intermediate risk; whilst the participants with nodules greater

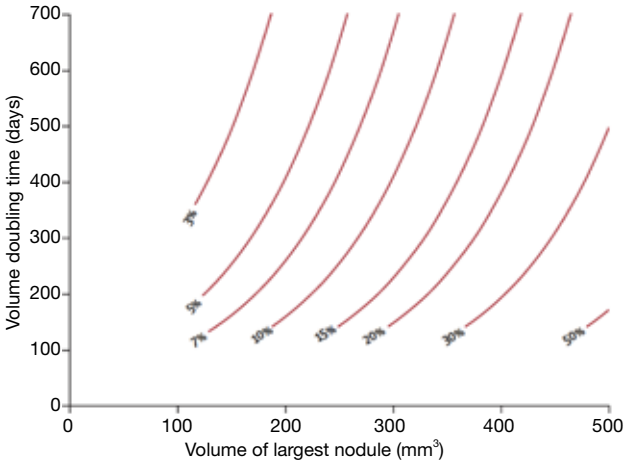

Figure 2 Contour plot of the effect of the combined effect of nodule volume and volume doubling time on 2-year lung cancer probability. The risk isolines represent the percentage of NELSON participants that will be diagnosed with lung cancer within 2 years according to the volume of their largest nodule and volume doubling time of the fastest growing nodule in the 50–500 mm^3 range. Reproduce from reference (21).

than 300 mm^3 had a significantly greater risk compared to no nodules (16.9%) and thus had a very high probability of developing lung cancer (21).

A very important message was provided on examining the NELSON volume doubling time data; the 2-year probability of developing lung cancer in patients with nodules measuring 50–100 mm^3 (or 4–5 mm diameter) was extremely low and did not significantly differ from patients with no CT scan detected nodules. This observation questions whether these individuals require yearly CT scans in a long term screening program and takes into account the harm and benefits for regular screening in such individuals; i.e., radiation exposure, psychological distress and cost effectiveness.

New pulmonary nodules at incident screens are now recognised as a clinical issue which has been analysed by Walters *et al*. (22). NELSON registered 1,222 new nodules in 787 participants. Fifty lung cancers were found, representing 4% of all new solid nodules and 34 (68%) lung cancers were diagnosed at stage I. They reported that the new nodules with <27, 27–206, 206 mm^3 were classified as low (0.5%), intermediate (3.1%) and high risk (16.9%) probability of developing lung cancer. The NELSON data showed that new solid nodules are detected at each screening round in 5%~7% of patients and have a significant probability of being malignant, even if they are of small size. These finding will have an impact on the way we develop our future screening guidelines.

The British Thoracic Society (BTS) has undertaken an in-depth piece of work developing guidelines on the management of pulmonary nodules (23). This work has been based on extensive review of the literature and the utilisation of recent publication from a number of lung cancer CT screening trials and in-depth analysis of data. A Guideline Development Group (GDG) was assembled utilising new research evidence, they have provided four management algorithms and the have included two malignancy prediction calculators (already discussed in this article) (*Figure 3*). Furthermore, volumetry has been recommended by BTA as the preferred measurement method of CT detected nodules and they also provided recommendations for the management of nodules with extended volume doubling times.

The BTS guidelines provide recommendation on the use of further imaging, and the use of PET-CT information which can be incorporated into pulmonary risk models, as well as advice on biopsy and the threshold for treatment without histological confirmation. Finally, BTS provided advice on the information which should be given to patients on the management of pulmonary nodules.

Clearly, the field of pulmonary nodule management in CT screening continues to advance and with the recent publication on the risk of malignancy in new nodules which has highlighted the need to continuously refine the nodule management algorithms and that the new nodule risk data should be taken into account (24).

Lung cancer screening is now a reality in the USA, covered by the Center for Medicare and Medicaid, however, Europe and the rest of the world have not yet implemented national lung cancer CT screening programmes at the time of writing this article, as they await the publication of the NELSON trial, with its mortality and cost effectiveness data. There will be a range of challenges when each country starts to implement lung cancer screening programmes in Europe, which have already been identified (25) but we also need to ensure that the appropriate protocolled pulmonary nodule management pathways such as the BTS recommendations are agreed and put in place, in order that we achieve the greatest clinical impact from future lung cancer screening programmes.

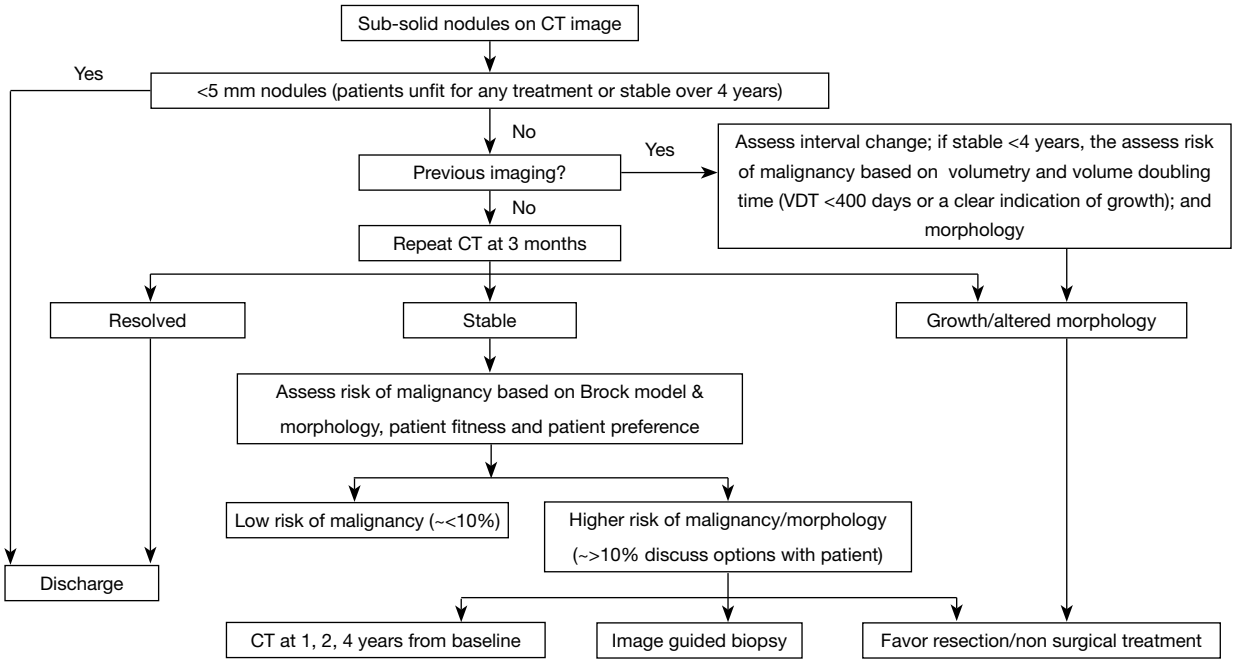

Figure 3 Management of pulmonary nodules. Redrawn from reference (23).

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Evaluation of pulmonary nodules in Asian population

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Background: American College of Chest Physicians (ACCP) provides guidelines to manage pulmonary nodules. Pulmonary nodules however can be malignant or benign. Similar incidence of tuberculosis (TB) and lung cancer in Asian countries raises concern over the relevance of suggested guidelines in Asian population. There is little data on the pattern of clinical practice in the management of pulmonary nodules in Asian country (Singapore). Our study describes the current pattern of clinical practice in this area highlighting the variation in practice and discussing the potential reasons.

Methods: Retrospective review of the medical records of patients diagnosed with lung cancer in 2010.

Results: Sixty nodules were identified in 32 patients. Nodules were detected incidentally on routine imaging in 7 (21.9%) patients. TB contact tracing and pre-employment screening were common ways by which nodules were detected incidentally. Over one third (37.5%) were non-smokers. Majority of nodules were located in the upper lobes of right and left lung followed by right lower lobe (RLL). Only few patients 8 (25%) had positron emission tomography (PET) scan for staging purposes. There were no difference in survival between patients who presented with single, 747 (range, 25–1,840) days *vs.* multiple nodules 928 (range, 30–2,572) days, P=0.26. In a retrospective analysis of malignancy risk with the probability calculator, 62.5% patients were at low-moderate risk whilst 32.5% were at high risk.

Conclusions: The clinical practice of managing pulmonary nodules in Asian population differs from ACCP guidelines. None of the patient had pre-test probability calculated, and few had PET scan. This is because upper lobe predominance of lung cancer is identical to TB, non-smoking history does not have any weight in discounting malignancy risk where many of the Asian lung cancer patients are non-smokers, and the local endemicity of TB and its confounding effect on radiological findings of CT scan and PET scan.

Keywords: Nodule; cancer (lung); Asia; tuberculosis (TB); histoplasmosis

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Introduction

A solitary pulmonary nodule (SPN) is defined as rounded radiological opacity in the lungs measuring up to 3 cm in diameter, fully surrounded by pulmonary parenchyma, in the absence of atelectasis, mediastinal lymphadenopathy or pleural effusion (1). Pulmonary nodules are relatively common, and lung cancer screening trials in patients with high risk for lung cancer have reported prevalence of SPN of 8%~51%, with malignancy found in 1.1%~12% (1,2). In clinical practice, a pulmonary nodule may be detected incidentally on chest radiograph (CXR) or computed tomographic (CT) scan ordered for other reasons (3). With the increasing use of CT imaging, it is likely that the number of pulmonary nodules detected will continue to rise, with

the physician's primary concern of excluding malignancy. However, some of these SPN detected may be benign such as healed granulomas, active granulomatous infections such as tuberculosis (TB), hamartomas, and arterio-venous malformation (4) out of which TB is the most common disease presenting as nodule in the Asian population.

American College of Chest Physicians (ACCP) provides guideline based algorithm to manage pulmonary nodules (5). Are these algorithms relevant to Asian population, and can we, or do we manage our patients according to these algorithms? There is little data in our local population regarding presentation and management of pulmonary nodules in lung cancer patients. Our study describes the current pattern of clinical practice in the management of pulmonary nodules in Asian country (Singapore), highlighting the strengths and limitations of using ACCP guidelines in managing them.

Methods

The medical records for all patients diagnosed with lung cancer in 2010 were reviewed. Out of these, all patients presenting with a single SPN or multiple pulmonary nodules (MPN) were selected. A single SPN was defined as radiological opacity measuring up to 3 cm in diameter, fully surrounded by pulmonary parenchyma, in the absence of atelectasis, mediastinal lymphadenopathy or pleural effusion (1,6,7). MPN was defined as a dominant nodule with 1 or 2 more nodules as per the ACCP guidelines (5). All patients presenting with lung masses as defined as >3 cm in diameter were excluded. The study protocol was approved by the NHG Domain Specific Review Board (2015/00932) and was conducted in accordance with the Helsinki Declaration of 1964 (revised 2008). Due to retrospective nature of the study, the consent was waived.

Clinical data including age, gender, symptoms at presentation, and smoking history were collected. Characteristics of the pulmonary nodules including type, shape, size, location and number of nodules were recorded. Histological information, staging investigations, presence of distant metastasis, treatment and survival were also recorded.

We also assessed validity of a tool recommended by ACCP for estimating the probability of malignancy in pulmonary nodules retrospectively as described below (5):

Probability of malignancy =

$$-6.8272+(0.0391 \times \text{age})+(0.7917 \times \text{smoke})+(1.3388 \times \text{cancer})+(0.1274 \times \text{diameter})+(1.0407 \times \text{spiculation})+(0.7838 \times \text{location})$$

Data analysis

We used software (SPSS, version 17; SPSS, Chicago, Ill, USA) for all statistical analyses. Where applicable, the results were compared using a Wilcoxon two-sample test or Fisher exact test. P values were two sided and considered indicative of a significant difference if less than 0.05.

Results

In the absence of any local lung cancer screening program, TB contact screening and pre-employment or employment renewal screening CXR were the most common ways how the malignant nodules were detected incidentally in Singapore. Other ways were the radiograph done to evaluate respiratory symptoms, CT coronary angiogram done to evaluate cardiovascular symptoms, and CT abdomen or CT urogram done to evaluate abdominal and urological symptoms respectively (*Table 1*). Sixty nodules were detected in 32 patients. Such nodules commonly presented with the size of 1–3 cm in diameter than being sub-centimetre. These nodules were either solid, cavitating, or ground glass in appearance (*Figure 1*). With regards to location, nodules were more common in the right lung, with right upper lobe (RUL), left upper lobe (LUL) and right lower lobe (RLL) being frequently involved lobes and apico-posterior segment of LUL & apical and anterior segment of RUL being the most frequently involved segments (*Table 2*, *Figure 2*). Probability calculator was not used in the management of our patients. However, retrospective analysis revealed that the calculator assigned low/moderate risk of malignancy in 62.5% of patients and high risk in 32.5% of patients. About 37.5% of patients were never smokers in our cohort. Most common histological type of cancer found in such nodules was adenocarcinoma and staging was done by the combination of bone scan and brain scan instead of positron emission tomogram (PET) scan (*Table 3*). Lung cancer was surgically resectable in 63% of patients. Median survival until death or last follow up was 2.1 years. One year survival was 80% and 5-year survival was 10% with no difference between patients who presented with single or multiple nodules (*Table 4*, *Figure 3*).

Discussion

The clinical practice of managing pulmonary nodules in Asian population differed from the ACCP guidelines. None of the patient had pre-test probability calculated and

few had PET scan, the likely reason being endemicity of granulomatous diseases like TB.

In the assessment of a pulmonary nodule, ACCP recommends the calculation of pre-test probability of malignancy (5). However, its performance in the Asian population remains to be determined. This equation or calculator uses "smoking" as one of the predictors of malignancy (5). However, in the current study 37.5% of patients were never smokers. A total of 31.6% of lung cancer patients and 54.5% of lung cancer patients with adenocarcinoma histology have been reported as never smokers in Singapore (8). This data is consistent with other studies in Asian population (9-11). Hence, in one third of the lung cancer patients and half of the adenocarcinoma lung patients, keying in "0" for smoking in the calculator, this predictor may falsely diminish contribution toward predicting malignancy.

Table 1 General characteristics of the patients (n=32)

Variables	Median (range) or N (%)
Total pulmonary nodule	60
Demographics	
Median age [(range), years]	71 [41-93]
Gender: male	19 (59.3%)
Smoking history	
Never smoker	12 (37.5)
Former smoker	11 (34.4)
Current smoker	4 (12.5)
Unknown	5 (15.6)
Presentation	
Symptomatic	13 (40.6)
Cough	3 (9.3)
Chest tightness	2 (6.2)
Haemoptysis	2 (6.2)
Shortness of breath	1 (3.1)
Others	11 (34.3)
Asymptomatic	19 (59.4)
Incidental	7 (21.9)
TB contact screen/follow up	4 (12.5)
Persistent abnormal CXR	4 (12.5)
Pre-employment	2 (6.25)
Unknown	2 (6.25)

TB, tuberculosis, CXR, chest radiograph.

Another predictor in the recommended probability calculator is the "upper lobe location" of the nodule (5). In our cohort, nodules were located more frequently in the upper lobes. However TB is also known to affects upper lobes more commonly than the lower lobes (12). This has implications. For example, both the number of new cases, and the age at onset of pulmonary TB and lung cancer are similar in Singapore. New cases of pulmonary TB between year 2009 and 2012 being 937, 951, 977, and 1,206 per year (13), and average number of lung cancer cases being 1,311 patients per year, in the same period (14). Similarly, age at onset for both the diseases is 5th decade onward. Hence, this predictor of "upper lobe location" may falsely contribute toward predicting malignancy in a benign nodule from TB in Asian population.

Another challenge this near equal incidence of the two diseases pose is that, TB being historically a well-known disease, the similarities in the incidence rates, similar clinical presentation such as weight loss, cough etc., and similar radiological features of the involvement of the upper

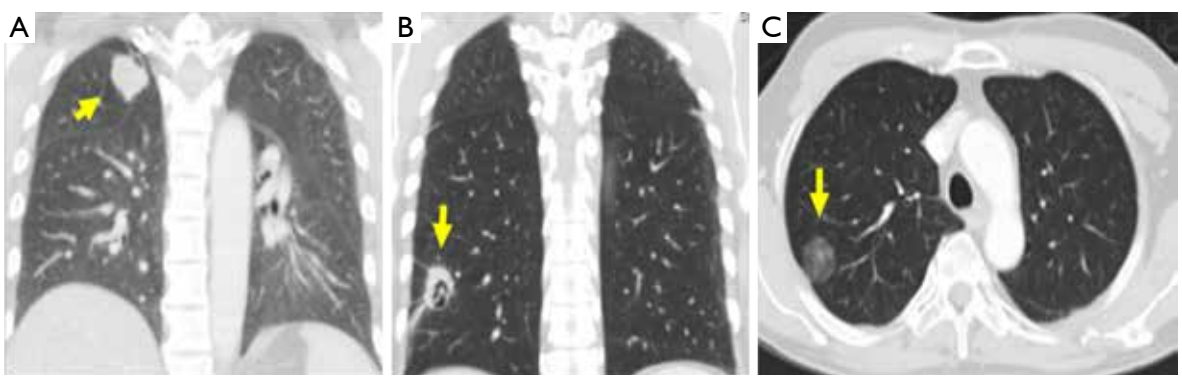
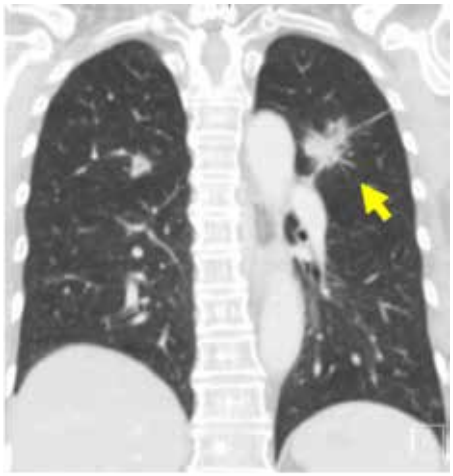


Figure 1 Type of nodules. (A) Solid; (B) cavitating; (C) ground glass nodule.

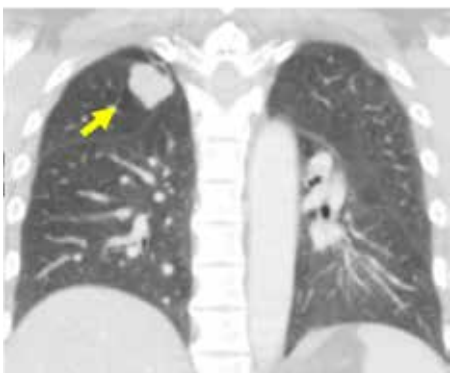
Table 2 Radiological features

Pulmonary nodule characteristics	N (%)
Size (cm)	
<1	26 (43.3)
1–3	34 (57.7)
Multiplicity	
Single	19 (59.4)
Multiple	13 (40.6)
Nodule shape	
Spiculated	16 (50.0)
Lobulated	13 (40.6)
Irregular	3 (9.4)
Nodule type	
Solid	44 (73.3)
Cavitating	6 (10.0)
Ground glass opacity	10 (16.7)
Nodule location (by lobes)	
Right lung	31 (51.7)
RUL	15 (25.0)
Right middle lobe	2 (3.3)
RLL	14 (23.3)
Left lung	29 (48.3)
LUL	14 (23.3)
Lingula	5 (8.3)
Left lower lobe	10 (16.7)
Nodule location (by segments)	
Apico-posterior segment of LUL	6 (10)
Anterior segment of RUL	4 (6.6)
Superior segment of LLL	4 (6.6)
Posterior basal segment of RLL	4 (6.6)
Apical segment of RUL	3 (5)
Posterior segment of RUL	2 (3.3)
Inferior segment of Lingula	2 (3.3)
Ant basal segment of LLL	1 (1.6)
Ant basal segment of RLL	1 (1.6)
Lateral basal segment of RLL	1 (1.6)
Posterior basal segment of LLL	1 (1.6)
Post segment of RUL	1 (1.6)
Superior segment of RLL	1 (1.6)
Superior segment of lingula	1 (1.6)

LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RLL, right lower lobe.



Spiculated



Lobulated

Figure 2 Lobar distribution of nodules and shape.

lobes, a primary physician is often led to suspect pulmonary TB first in a patient with a pulmonary nodule, often leading to misdiagnosis of lung cancer as TB. Correspondingly, reporting radiologist mentioning suspicion of TB in their report may also contribute to misdiagnosis since in clinical practice, physicians rely on the "report of the radiograph" more than the radiograph itself. Singh *et al.* reported 14 out of 70 lung cancer patients being misdiagnosed and treated inappropriately for TB for a mean duration of approximately 4 months (15). In our own audit of a cohort of 54 patients who were referred to respiratory physician for CXR abnormality and were eventually diagnosed with lung cancer, the diagnosis of lung cancer was missed or delayed in 24/54 (44.4%) patients as they were initially suspected to have TB based on the radiograph. Never smoking patients

Table 3 Investigation and treatment of malignant pulmonary nodules

Variables	Median (range) or N (%)
Diagnostic procedure	
TTNA	26 (81.2)
Bronchoscopy	2 (6.2)
Histology	
Adenocarcinoma	20 (62.5)
NSCLC	5 (15.6)
Squamous cell carcinoma	1 (3.1)
Others	3 (9.4)
Unknown	3 (9.4)
Pre-test probability	
Median (range)	51.7% (8.36–90.08)
5%~65%	20 (62.5)
>65%	12 (37.5)
Staging investigation	
Brain imaging	20 (62.5)
PET scan	8 (25.0)
Bone scan	11 (34.4)
Metastasis	
Distant metastasis	4 (12.5)
No distant metastasis	28 (87.5)
Recommended treatment	
Surgical	20 (62.5)
Underwent surgery	17 (53.1)
Declined surgery	3 (9.4)
Non-surgical	12 (37.5)
Chemotherapy	4 (12.5)
Radiotherapy	1 (3.1)
Tyrosine kinase inhibitors	4 (12.5)
Conservative	3 (9.4)
Mutation status	
Exon 18	2 [8]
Exon 19	4 [16]
Exon 20	1 [4]
Exon 21	3 [12]

with nodular changes on the CXR, and CXR reported as infective changes suspicious of TB by the reporting radiologists, correlated with the occurrences of misdiagnosis (unpublished data). Since it may take two months (waiting time of TB culture) before TB is confirmed or excluded, this misdiagnosis leads to delay in diagnosis and patient dissatisfaction.

With significant proportion of never smokers developing cancer, and significant proportion of patients with upper lobe involvement secondary to TB in a population with the near equal incidence of TB and cancer, it is arguable that the probability calculator may give inaccurate result in Asian population and assign disproportionately high risk of malignancy to benign nodules.

Following calculation of the pre-test probability, ACCP guidelines recommend PET scan prior to non-surgical or surgical biopsy for nodules between 8–30 mm (5). This was not practiced in our population. The PET was done in only 25% of patients in our cohort with the intent of staging after the histological diagnosis and it was "true negative" for distant metastasis in all 8 patients. This illustrates that physicians only trusted the PET scan for staging and not for diagnosis. The near equal incidence of TB and lung cancer in Asian population poses challenge to the recommendation of PET scan. In Western countries like USA, the incidence of infective granulomatous diseases such as TB and histoplasmosis, which can lead to confounding radiological changes that mimic malignant nodules is 3.7 in 100,000 and 1 in 100,000 respectively (16,17). Whereas in Singapore, the incidence of TB is 30.7 per 100,000—10 times that of USA (13,18). This pattern increases the chance of false positive PET scan in local population, making the pre-test probability of a positive PET scan being equally from infective and malignant pathology, rendering it less relevant in Asian population.

Regarding screening, although low dose CT screening has shown mortality benefit, however one of the inclusion criteria for lung cancer screening based on National Lung Cancer Screening Trial (NSLT) is smoking history (19). Eligible patients are those between 55 and 74 years of age with a history of cigarette smoking of at least 30 pack-years, and, if former smokers, had quit within the previous 15 years (19). Since 30%~40% of Asian population with lung cancer is never-smoker, it makes approximately one third of the lung cancer patients ineligible for screening, limiting the adoption of lung cancer screening to local population (20).

Regarding survival, the reported expected 5-year survival of stage-I disease is 65% (21). However, the 5-year survival in our cohort was 10%. Our local data on 5-year survival in stage-I shows the survival in lung cancer to be 50%. The lower 5-year survival in our cohort can be explained by the 4 (12.5%) patients having metastatic disease, 3 (9.4%)

Table 4 Subgroup analysis of solitary pulmonary nodule and multiple pulmonary nodules

Variables	SPN (N=19) (n, %)	MPN (N=13) (n, %)	P value
Males	9 (47.0)	10 (76.9)	0.14
Age median [range, years]	69 [41–93]	71 [60–81]	1
Pulmonary tuberculosis	4 (21.1)	3 (23.1)	1
Pre-test probability (range, %)	56.92 (8.36–90.08)	41.43 (3.88–81.69)	0.14
Smoking history			
Never smoker	9 (47.3)	6 (46.1)	1
Ex & current smoker	10 (52.6)	7 (53.8)	1
Histology			
Adenocarcinoma	12 (63.1)	9 (69.2)	1
Squamous cell carcinoma	1 (5.2)	0	1
Mutation done	15 (78.9)	10 (76.9)	
Mutation detected	6 (40.0)	4 (40.0)	1
Treatment			
Surgical	10 (52.6)	7 (53.8)	1
Non-surgical			
Chemotherapy	6 (31.5)	6 (46.1)	0.43
Radiotherapy	6 (31.5)	3 (23.0)	0.67
Tyrosine kinase inhibitors	5 (26.3)	5 (38.4)	0.69
Nodule location			
Right lung			
RUL	4 (21.1)	11 (84.6)	0.008
Right middle lobe	0	2 (15.3)	0.15
RLL	4 (21.1)	10 (76.9)	0.003
Left lung			
LUL	7 (36.8)	7 (53.8)	0.47
Lingula	0	5 (38.5)	0.006
Left lower lobe	4 (21.1)	6 (46.2)	0.24
Nodule type			
Solid	15 (78.9)	6 (46.2)	0.07
Cavitating	4 (21.1)	2 (15.4)	0.26
Ground glass opacity	0	10 (76.9)	0.0001
Survival [days]	747 [25–1,840]	928 [30–2,572]	0.26

SPN, solitary pulmonary nodule; MPN, multiple pulmonary nodules; RUL, right upper lobe; RLL, right lower lobe; LUL, left upper lobe.

patients refusing surgery despite being resectable, 2 (6.2%) patients underwent surgery but were upstaged at the time of surgery, and 1 (3.1%) patient lung cancer progressed despite surgery. However, there was no difference in survival between our patients presenting with SPN or MPN. They had similar demographics, histology and treatment received. Therefore patient presenting with MPN should not be presumed metastatic and denied appropriate treatment, as survival is equal in comparison to a SPN. This is consistent with recommendations from British Thoracic Society and ACCP that coexistent nodules in patients with lung cancer should not be presumed to be malignant, especially in patients who otherwise would be a surgical candidate (5,22).

In addition to ACCP guidelines, other societies that

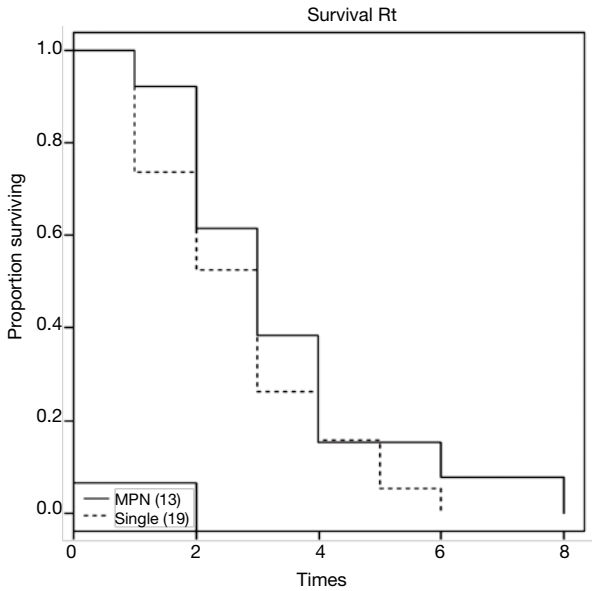


Figure 3 Kaplan-Meier survival curve in patients with single pulmonary nodule and MPNs. MPN, multiple pulmonary nodule.

provide guidelines on the management of pulmonary nodules are Fleischner Society and British Thoracic Society. Fleischner Society, similar to ACCP guidelines, emphasizes distinguishing the patients into high risk and low risk groups based on "smoking" history. No follow-up in ≤4 mm, follow up CT at 1 year in >4–6 mm, or 6 months in >6–8 mm sub-centimetres nodules is recommended for never smokers (6). Similarly, British Thoracic Society stresses on emphysema as one of the items in their proposed prediction model (22). The appropriateness of these criteria is debatable in the context of 50% of patients with adenocarcinoma (most prevalent subtype of lung cancer) being never smokers in Asian population.

Our study has following limitations. First, it is a retrospective study limited by unavailability of information on certain variables, with small population enrolled. Second, we only included patients with malignant nodules. This may have introduced selection bias. The inclusion of non-malignant nodules would have provided greater information on the false positivity or false negativity and the accuracy of the PET scan and CT scan. However, our aim was to study the pattern of local practice in the management of lung nodules that turn out to be malignant.

Recommendation

We propose the following algorithm when evaluating a patient with pulmonary nodule in our local population. In all patients with a newly discovered pulmonary nodule and no old CXR s or CT scans for comparison, an early CT is recommended for accurate characterization of the nodule's size, shape, type, and determination of the best diagnostic approach. Two specimens of sputum should also be sent for AFB smear and TB culture at the first visit to exclude pulmonary TB. Pre-test probability of malignancy should be estimated after the CT scan with a validated tool. All patients with moderate or high probability for malignancy should be offered further investigation to obtain histological "and" microbiological samples. Appropriate diagnostic investigation would depend on findings of CT with transbronchial lung biopsy with or without radial probe endobronchial ultrasound preferred for nodules >1 cm with bronchus sign, and transthoracic needle aspiration or assistive technologies like navigation bronchoscopy preferred for peripherally located nodules <2 cm with no bronchus sign, and wedge resection or surveillance CT scans for nodules <1 cm in diameter. With every diagnostic method, specimen should be sent both for AFB smear and TB culture along with histological examination.

In conclusion, the clinical practice of managing pulmonary nodules in Asian countries may differ from the ACCP guidelines. This is most likely secondary to the local endemicity of TB and its confounding effect on radiological findings of CT scan and PET scan. Factors like being responsible for most number of cancer related deaths in Singapore, reasonably high incidence of ~1,500 patients per year, presentation in late stage, and lack of modifiable factors to prevent cancer, demand an aggressive approach to management of lung cancer. This can be achieved by formation of, first, locally relevant screening programs and guidelines that include never smokers, and incorporate epidemiological patterns of granulomatous infections. Second, developing clinical management protocols to ensure adequacy of tissue to allow mutation analysis for each patient, and promoting increased and easy adoption of mutation analysis due to higher prevalence of EGFR sensitive population in Asia. Third, encourage research to identify methods to distinguish between benign and malignant nodules non-invasively i.e., radiologically with precision.

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Footnote

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Comments on characterization of solitary pulmonary nodules with 18F-FDG PET/CT relative activity distribution analysis

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Background

The solitary pulmonary nodule (SPN) is defined as focal parenchymal opacity of the lung, <3 cm in size, generally discovered incidentally during an X-rays examination (1), with a prevalence of 2.1% in non-selected populations. Subsequently, SPNs may be classified by computed tomography (CT), allowing better radiographic criteria as margins, size, density, contrast enhancement and calcification pattern (2), in order to ensure the diagnosis and correct identification between malignant lesions (metastases, primary tumors) and benign nodules (granulomas, abscess, vascular malformations). Despite these forewords, the correct diagnosis of SPNs by means of morphological criteria still represents a diagnostic dilemma (3).

As a matter of debate, the attention of the researchers has been focused during the time on the best diagnostic tool with the highest accuracy in distinguishing SPNs with a benign behavior from those with a prospective of malignancy, setting undeniable repercussions regarding the choice of the best treatment option, patients prognosis and overall costs of management for the community (4). In particular, these forewords are of the utmost importance when we account that a SPN can be a primary localization of lung cancer: one of the most diffuse causes of death in the United States and in the rest of the world (5), with evident social repercussions linked to the cause-effect relationship with tabagism and environmental exposure and the high costs in the overall sanitary management of this disease. In fact, lung cancer remains in the top leading cause of cancer death in both men and women, despite an extensive list of risk factors has been well-characterized with variability between leading causes (6).

On the other hand is intuitive, prior to be scientifically proven, the absolutely negative impact that could sort a wrong diagnosis on the life quality of patients with benign lung lesions not correctly identified.

In this scenario, it is evident that the early correct identification of SPN can sort positive effects on the patients care, in terms of correct choice of the best treatment option and on the disease-free survival in patients with malignant lesions, considering that an important percentage (30%~40%) of SPNs is malignant (7).

As a matter of fact, the attention of researchers is focused on the early diagnosis of malignant SPNs, by means of the best imaging modality option. Beyond the limited utility, X-rays, due to the widely diffusion and the easily reproducibility, still remain the first imaging step in diagnosing SPNs, although often the diagnosis occur as an incidental finding during the asymptomatic phase. The CT of the thorax has become the best imaging tool for a rapid, relatively not-expensive correct anatomical characterization of the whole thoracic district, from the pulmonary interstitium to the upper airways, offering a rapid, high resolution multi-planar evaluation of lungs and mediastinal tissues. Furthermore, the use of contrast agent can improve the visualization of the lung parenchyma by

increasing the absolute CT attenuation difference between the target and surrounding tissues, helping to depict lesions with more accuracy (8). Despite this fact, are also well known the limits of CT in depicting lung lesions smaller than 3 cm, by assessing only the morphological, especially in some complicated radiologic scenarios as the "honeycomb lung" (9). In the last two decades, positron emission tomography (PET) has been tested to enlarge the field of the early diagnosis and correct identification of SPN with a better depiction of the molecular processes at the basis of the metabolic behavior of the lesions. PET with 18F-FDG is widely useful for SPNs characterization due to the intrinsic properties of the tracer as analogue of the glucose, surrogate marker of cells vitality and biological cells behavior. Therefore, the metabolic assessment of SPNs was one of the first useful indications of this 18F-FDG PET (10), showing promising results in the correct diagnosis of SPNs, by means of both visual assessment and semi-quantitative evaluation with calculation of the "differential uptake ratio" (DUR) in the lesions, allowing a sensitivity of 95% and a specificity of 80% (11). Despite these data were obtained on a non-hybrid PET scanner, often using as standard of reference the clinical criteria of Bayesian analysis, the probability of diagnosing cancer using the "standard criteria" available in literature ("*based on patient's age, history of previous malignancy, smoking history, size and age of nodule and presence or absence of calcifications*") also using histologic sample as the gold standard (12). Therefore, PET alone was more accurate in depicting the likelihood of malignancy of lung nodules, in comparison with standard criteria.

During the time, the development of hybrid PET/CT scanners allowed to define more accurate exams, in order to take advantages of the high sensitivity provided by PET with a more specificity with the morphologic characterization of CT, the "hybrid scanners era" started with the encouraging results, in terms of global accuracy, of the experiences of various group of researchers (13,14), improving the added value of an integrated evaluation between metabolic data and morphologic features of the lesions. More specifically, the evaluation of PET data ensured the usefulness of semi-quantitative analysis of the maximum standardized uptake value (SUVmax) (15), a measure of the metabolic activity inside the lesions, provided by the ratio between administered tracer and weight of the patient, obtained by the following Eq [1] (16):

[Radioactivity (kBq)–tissue volume (mL)]/[dose administered (kBq)/body weight (g)] [1].

In particular, a large series of studies demonstrated that a SUVmax cut-off value of 2.5 was able to discriminate between malignant from benign lesions, since malignant lesions show an increased metabolic activity, with a SUVmax generally higher than 2.5, allowing an increase of the positive predictive value of 18F-FDG PET (17-20).

Despite these promising results, the aim of the researchers was focalized in reducing the rate of false negative and false positive cases in PET/CT, by using both semi-quantitative analysis and morphologic criteria of the CT component of the exam, with the help of the measurement in Hounsfield Units of the enhancement of the iodinate contrast agent inside the cells, allowing a relatively cost-effective approach to evaluate the SPNs (4) and a rise of specificity.

Moreover, based on the evidence that metabolic activity of cancer cells tends to rise during the time, various groups of researchers tried to better depict SPNs behavior with a dual time PET acquisition protocol, since in the late acquisition it was possible to observe that benign lesions moderately 18F-FDG avid, such as pulmonary mycobacteriosis (21), present lower SUVmax than in the early scan while cancer cells can display a rise of the uptake (22).

In particular, in the experience of our group with dual-time acquisition point 18F-FDG and concomitant contrast enhanced CT, the early and delayed SUVmax of malignant lesions were higher than those of benign nodules, the contrast enhanced CT did not show meaningful accuracy whereas the dual-time point SUVmax was associated only with the better value of sensitivity (83%) (23). Therefore, also the role of the dual time point PET and of the enhanced CT is still under exam and better non-invasive methods of assessment are still required.

18F-FDG PET/CT relative activity distribution (RAD) analysis of SPNs: our comments

Another chapter in the molecular imaging of SPNs was recently provided by the work of Zhao *et al.* (24): the aim of this study was to compare the capability of a new semi-quantitative index of 18F-FDG uptake in the cells, the relative activity distribution (RAD), with the typical markers, in differentiating benign and malignant SPNs, by means of 18F-FDG PET/CT.

Foremost, the authors developed the concept of RAD. Since cancer cells tend to invade blood vessels, they supposed that the metabolic activity detectable by 18F-FDG uptake should be higher in the proximal part than in the distal part of malignant SPNs, using the ipsilateral hilar

angle as the reference point. To verify this hypothesis, they analyzed a population of 175 patients, measuring in all cases: the RAD-index, SUVmax, SUVmax corrected for partial volume (corrSUVmax) and retention index (RI), correlating these data also with the visual assessment.

Therefore, the malignant lesions showed a meaningful lower RAD index than benign lesions. Furthermore, the area under the curve (AUC) was significantly larger and specificity was significantly higher for RAD than for SUVmax, corrSUVmax and visual assessment. Moreover, the RAD analysis showed the best sensitivity value (92%), with the exception of visual assessment, performed by two physicians with more than 8 years of experience in this field. Consequently, the analysis of RAD index showed meaningful differences between malignant and benign nodules.

For our opinion, the best added value improved by this index is the better value of specificity, that is the goal of the hybrid PET/CT evaluation of lung nodules, it being well understood that the visual or semi-quantitative analysis of the 18F-FDG inside the cells is usually associated with satisfying values of sensitivity (20). Moreover, the RAD analysis takes into account the heterogeneity of the cancer lesions, showing different phenotypically and functionally cells, with a dynamic approach in depicting the biological heterogeneity of the lesions.

An important feature of the RAD analysis is the tendency to remain an accurate semi-quantitative index of objective analysis of the uptake in the cells, without invalidate the evaluation of the lesion, considering the rigid adopted inclusion criteria and the easily reproducibility of the exams. The only potential limit of this approach is the measure of the ipsilateral pulmonary hilar angle, which can present intra-observers variations, especially when we consider some errors potentially induced by the respiratory movement, in particular in those SPNs localized in the inferior lobes of the lungs, particularly interested by respiratory excursion.

However, the development of respiratory-gated PET imaging (25) could improve this aspect, allowing a better accuracy of the overall metabolic evaluation of SPNs, particularly with the measurement of RAD index, improving the detectability and semi-quantitative evaluation of even small SPNs, especially considering the high number of SPNs smaller than 1.5 cm in diameter (34%) evaluated in the present study by Zhao *et al.* (24).

Despite the promising results, another potential limit of this cited paper is the relatively high number of examined malignant lesions (65%), in comparison with the experience of other groups in this field (10,11,13,14). This high percentage of malignant lesions was also recently reported in a paper by van Gómez López *et al.* (26). The authors examined 55 patients with 18F-FDG PET/CT. Among these, 40 (72.7%) were malignant. Similar to the paper of Zhao *et al.* (24), the aim of this study was to assess the capability of new semi-quantitative methods of quantization of the metabolic activity inside the cells. Otherwise, they did not find meaningful diagnostic impact for these new parameters, as SUVmax threshold depending on SPN diameter or ratio SUVmax/diameter of the lesion (26), conversely, similarly to the experience of Zhao *et al.*, confirmed the undisputed role of visual evaluation of detectable metabolism as the "method" with the best accuracy in discriminating between malignant and benign lesions.

For these reasons, we need to underline two important features: as first, the necessity of an adequate visual evaluation of PET/CT scans of patients with SPNs by nuclear physicians or radiologists with expertise in the field of thoracic disease, in order to take advantage of the overall amount of data or clinical suggestions provided by PET and CT simultaneously, in a way of mutual strengthening of diagnostic accuracy between the two techniques. Of course, it is also important the knowledge of morphological features on CT and radiological criteria to correctly identify non-18F-FDG-avid lesions with characteristics of malignancy as well as avid 18F-FDG nodules showing high tracer uptake, with benign behavior (27).

The second consideration concerns the improvement of the specificity provided by RAD index analysis in evaluating SPNs, probably the main suggestion provided by the work of Zhao *et al.* (24). In fact, the attempts of researchers on this topic were focused on the necessity to rise the global accuracy of PET/CT evaluation, it being clear the evident high sensitivity of 18F-FDG PET/CT since the first studies (10,11).

However, future studies on larger populations are needed to define results and to deep the scientific reputation of this new semi-quantitative approach to clearly split malignant SPNs, needing of rapid use of surgical and/or systemic therapy, from benign lesions, in whom medical therapy is requested or long-term follow-up can be sufficient for the health of the patients. In particular, the field of interest of this new approach should be extended to the study of lung cancer with associated infectious lung diseases, a topic where the 18F-FDG PET/CT traditionally may not accurately descript malignant lesions (28).

As a future trends, we must consider that the recent fast

increasing availability of hybrid PET/magnetic resonance imaging (MRI) scanners will also improve this trend of research, permitting to take advantage of the best quality of images provided by MRI and its highest power resolution limit, to develop more accurate methods of quantization of the tracer uptake inside the cells, also permitting a more precise placing of regions of interest for calculating RAD index or other semi-quantitative parameters of uptake, with or without the contrast agent administration, as recently described (29,30). In fact, the added value of MRI lies in its multiplanar capabilities, which may allow for a better depiction of lung structures, with the advantage of a higher spatial resolution. In addition, any morphological abnormality may also be better depicted after the administration of contrast agent. About this trend, an important suggestion could be to improve the impact of RAD analysis with a dual time point PET/MRI scan.

Finally, once confirmed its usefulness in the management of SPNs, as future field of application, it would be interesting to deep the knowledge of the role of RAD index in identifying the T component of somatic tumors in order to ensure features as the exact recognition of the site of the biopsy or, considering the intrinsic considerations linked to the potential better depiction of the tumor vitality, to define the response to therapy of particular lung lesions, in particular referring to radiotherapy.

In conclusion, we can state that the variable panorama of semi-quantitative models of tracer uptake quantization in tumor lesions has been enhanced by a novel promising approach, the RAD index, which needs to be rapidly further evaluated. The challenge is open.

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Footnote

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^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography characterization of solitary pulmonary nodules: can we do better?

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Solitary pulmonary nodules (SPNs) are discrete, well-marginated, rounded opacities less than or equal to 3 cm in diameter that are surrounded by lung parenchyma, do not touch the hilum or mediastinum, and are not associated with adenopathy, atelectasis, or pleural effusion. These structures have a high prevalence, being visualized in up to 69% of patients screened using low-dose computed tomography (CT) (1).

Whether detected serendipitously or during routine investigations, SPNs raise the questions of their benign or malignant character and what are the optimal actions to perform: observation, investigation or resection.

In the early 1990s, it was hypothesized that malignant and benign pulmonary nodules have distinctly different physiologic, metabolic, and pharmacokinetic characteristics. Many attempts have been made to differentiate these two nodule types with dynamic single-detector helical and multi-detector CT, dynamic magnetic resonance imaging (MRI), positron emission tomography (PET) or combined PET/CT with use of fluorine ^{18}F-fluorodeoxyglucose (FDG). However, despite many studies considering the problem, the correct diagnosis of SPNs remains a challenge to clinicians, radiologists and nuclear medicine physicians. Up to now, neither their morphology, contrast enhancement properties nor metabolism are specific enough to discriminate benign from malignant lesions (2,3). This explains why malignant lesions account for only 60% of resected pulmonary nodules in some series (4).

With respect to the diagnostic accuracy of imaging techniques, no differences have been found among dynamic contrast-enhanced CT, MRI, FDG-PET and technetium 99 m (99 mTc) depreotide single photon emission computed tomography (SPECT), for evaluation of SPNs (5). Although all of those diagnostic methods have high sensitivities, their specificities are intermediate (5,6), what limits the application of the techniques.

In order to improve the specificity, some dynamic aspects of perfusion and metabolism have been explored with the development of new imaging procedures. Dynamic first-pass contrast enhanced perfusion area-detector CT has been described as more specific and accurate technique for the differentiation between malignant and benign pulmonary nodule groups than MRI and integrated PET/CT (7,8). With respect to metabolism, a meta-analysis by Barger *et al.* (9) found the additive value of dual time point FDG-PET questionable because of significant overlap of benign and malignant nodule characteristics.

Focusing on metabolism, the evaluation of pulmonary nodules by FDG-PET has been limited because of several factors involved in the FDG distribution: (I) the maximum standardized uptake value (SUVmax), as reflection of the degree of FDG uptake, is not a specific marker of malignancies; (II) SUVmax is affected by a large number of methodological factors, which are difficult to control (10);

(III) small lesions are challenging due to PET's limited spatial resolution, resulting in partial-volume effect; (IV) lung fields are in continuous movement, what causes an important detriment in the metabolic detection of SPNs, especially in smaller lesions; (V) the biological characteristics of malignant and benign lesions affect FDG distribution.

The referred conditions influence the lesion metabolic detection and its interpretation. This has resulted in a lack of consensus criteria for defining quantitative thresholds to classify SPNs as malignant or benign. Much research has been devoted to overcome the above mentioned limitations. However, the attempts to palliate respiratory movement effect, as 4-dimensional FDG PET/CT or deep-inspiration breath-hold PET/CT, or methods of correction of partial volume effect to obtain the corrected (corr) SUVmax, have not reported a significant advantage and do not take into account other factors such as tumor density, FDG avidity, and background activity, that play a role in semiquantitative parameters (11-13). Furthermore, although these procedures provide a more realistic semiquantitative value in SPNs, SUVmax increases both in malignant and benign lesions. Therefore, lesion classification using semiquantitative approaches is still controversial.

In principle, although controversy exists, FDG uptake could be expected naively to be correlated with the biological aggressiveness and clinical behavior of malignant lesions. Thus, this is another factor to consider, adding complexity to the metabolic evaluation of SPNs (10,14).

In a recent work, Zhao *et al*. (15), conjecture that cell's metabolic activity may be expected to be higher in the proximal part than in the distal part of malignant SPNs due to the vascular supply of hilar region. To test their hypothesis they analysed the intralesional FDG distribution and introduced a novel semi-quantitative measure: the relative activity distribution (RAD) index, in order to assess its goal for SPNs characterization. To calculate the RAD index, Regions of interest (ROIs) were placed first on hilar angle in order to define a reference point in its center. ROIs were also placed on the SPNs. For the SPN, all voxels with activity ≥90%, ≥80% and ≥70% of SUVmax were automatically segmented and their average coordinates set the lesion reference points as O90, O80 and O70. Distances (*d*) from the lesion reference points O90, O80 and O70 to the hilar reference point were calculated and divided to obtain the RAD index as the first quotient in the series *d*90/*d*80, *d*80/*d*70, … that was possible to compute. Geometrically, this index intends to measure in a very simple way, the asymmetry of the peak of the FDG distribution with respect to the direction of the hilar reference point.

Zhao and co-workers (15) claim that the RAD index enables a more specific and accurate differentiation between malignant and benign SPNs than SUVmax, corr SUVmax and retention index. In their study they find no significant differences in sensitivity and accuracy compared with visual assessment, but the main advantage of the method is that it was more specific than visual assessment. Furthermore, RAD index calculation can be easily automatized, and is reproducible and objective. They stated that the cited index might be beneficial for SPNs characterization with the best statistical cut-off value of 0.99, in order to differentiate malignant and benign SPNs.

However, before this index can move into mainstream use in the clinics, some considerations about the study and/or the definition of the RAD index should be addressed in further works by researchers in this field.

First, RAD index is defined as a quotient of two distances that are very close (a fraction of the SPN size) in relation to their absolute values (distance to the lesion to the hilar reference point). This implies that index values are all clustered around 1, slightly below 1 for malignant nodules and slightly above 1 for benign ones. A definition of the index taking differences of distances in units of the SPN size [e.g., (d90-d80)/SPN size)] would provide better spread values and have a direct interpretation as a fractional deviation of the high FDG uptake peak from the "geometrical" center.

Also, from the statistical point of view, the RAD values for malignant nodules were 0.98±0.03 while for benign RAD indexes were 1.01±0.02. Although the authors claim that statistical differences were significant, that assertion seems to contradict the fact that both confidence intervals are fully overlapping. More evidences and a deeper statistical analysis should be provided in support of the author's claims.

As a third comment, the lesion points taken as reference (O90 and O80 or O80 and O70) are locations of high FDG metabolic activity. According to our understanding, these selected points have similar metabolic characteristics and the effect of noise, the fact that small nodules have a very limited number of voxels, and other factors might substantially influence the results. It would be interesting to understand why those factors did not influence Zhao *et al.*'s data and if other, in principle more robust definitions of similar indexes could be constructed. For instance

definitions accounting for ratios between regions of high and medium metabolic activities could lead to alternative definitions of similar indexes. Also, indexes defined by integrals over the whole metabolic activity distribution along the line pointing to the hilar reference point would probably be more robust definitions of asymmetry.

On the other hand, the hypothesis that malignant nodules grow towards blood vessels needs further study because although in the avascular phase, malignant tumors do not have the potential to generate vessels and contain only a few preexisting vessels encased by the tumor growth, new tumor vessels develop as the result of stimulation of angiogenic factors. Thus neoangiogenesis plays an important role in the tumor growth. Besides, the effects of such functional mechanism cannot be spatially uniform throughout the tumor, what causes multiple vascular patterns (16,17). Furthermore, in inflammatory nodules, the processes of increased blood flow and permeability of vessels depend on the stage of the inflammatory process.

Additionally, although the most prevalent malignant group was constituted by adenocarcinomas, different biologically malignant lesions were analysed (minimally invasive adenocarcinomas, adenocarcinomas *in situ*, invasive adenocarcinomas, squamous cell carcinomas, neuroendocrine tumor, sarcomatoid carcinoma, and metastatic lung tumors) what may lead to a wide variety of growth patterns. This heterogeneity in the population of malignant SPNs studied is an important limitation to obtain reliable results. May be some types of cancers are more prone to satisfy the authors hypothesis?

It is also important to point out that the locations of SPNs were not reported. In centrally located SPNs, the mean SUVmax value could be significantly higher than in peripherally located ones. This higher SUVmax value may be associated with higher blood flow in central regions or higher ground activities of lung hilus and mediastinal organs (18). Thus lesion location, for example a central predominant location of malignant lesions, could have some influence in the intralesional distribution of FDG and hence in the obtained results.

Finally, respiratory movement can cause blurring. This effect averages out the measures uptake values of the voxels with higher uptake and can change the isocenter or the average coordinates locations, especially in small lesions. Thus, in addition to the potential difficulty in determining with precision the O90, O80, ... points, the blurring induced by respiration may limit the applicability of the method to small lesions. Zhao *et al*. comment that their sample had high percentage of malignant nodules with a large median lesion size, thus a larger sample is required to clarify the potential applicability of the method to small malignant lesions.

In summary, the interesting theory developed by Zhao *et al*. (15) that the tumor metabolic activity will be higher in the proximal part than in the distal part of malignant SPNs due to the vascular supply of hilar region, deserves more investigation. Although vascularity of tumor tissue and intratumoral microvessel density may be an important component in determining the glucose metabolic rate of a neoplasm, it is neither the only one nor it is exclusive of malignant lesions (19,20). The novel methodology and the RAD index or other similar ones to follow, when validated in more complete studies, may provide useful tools to solve the problem of identifying the malignancy of SPNs. Thus Zhao *et al.* work has the potential to have a substantial impact on the management of these diseases.

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Footnote

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Radiomics of pulmonary nodules and lung cancer

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Abstract: The large number of indeterminate pulmonary nodules encountered incidentally or during CT-based lung screening provides considerable diagnostic and management challenges. Conventional nodule evaluation relies on visually identifiable discriminators such as size and speculation. These visible nodule features are however small in number and subject to considerable interpretation variability. With the development of novel targeted therapies for lung cancer the diagnosis and characterization of early stage lung tumours has never been more important. Radiomics is a developing field aimed at deriving automated quantitative imaging features from medical images that can predict nodule and tumour behavior non-invasively. In contrast to conventional visual image features radiomics can extract substantially greater numbers of nodule features with much better reproducibility. This paper summarizes the basic process of radiomics and outlines why radiomic feature analysis may be particularly well suited to the evaluation of lung nodules. We review the current evidence for its clinical application with regards to pulmonary nodule management, considering promising applications such as predicting malignancy, histological subtyping, gene expression and post-treatment prognosis. Radiomics has the potential to transform the management of pulmonary nodules offering early diagnosis and personalized medicine using a method that is in cost-effective and non-invasive.

Keywords: Lung cancer; pulmonary nodules; radiology; radiomics; CT

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Introduction

The addition of the term "omics" to fields of science originates in basic science. It is now a widely used suffix in clinical medicine research to denote the concept of examining large volumes of complex data to identify precise characteristics or outcomes. In the setting of lung nodules and lung cancer, radiomics is aimed at deriving automated quantitative imaging features that can predict nodule and tumour behaviour non-invasively (1,2).

Pulmonary nodules are a frequently encountered incidental finding on CT, and the challenge for radiologist and clinicians is differentiating benign from malignant nodules. In current practice pulmonary nodules identified on CT are managed according to widely accepted guidelines (3-5). These guidelines recommend that nodules be ignored, kept under surveillance or undergo further testing. The prime driver behind nodule management is nodule size on the basis that the risk of lung cancer increases exponentially with nodule size (6-11). Additionally, a host of subjective visual signs that may predict malignancy have also been described. However, existing guidelines are subject to limitations: ultimately most small nodules require surveillance and it is challenging or even impossible to predict with certainty the likelihood of malignancy from a single CT. Furthermore, nodule evaluation based

on visual morphological signs (for example smoothness, irregularity and speculation), are subject to considerable interpretation and variability (12,13) and the number of visually identifiable discriminators in lung nodules is limited. By contrast, in radiomics the number of extractable nodule features is substantially greater and can be identified with far greater reproducibility. For example, in one study of lung cancer patients a total of 440 radiomic features were extracted (14) that were capable of predicting tumor histological subtype from a single time point CT.

The rationale for using radiomics in lung nodules

There are a number of reasons why the application of radiomic feature analysis may be particularly suited to the assessment and management of pulmonary nodules.

Accurately delineating a nodule from adjacent lung parenchyma and other structures is crucial if image features are to be assessed in a reproducible and robust fashion. In the case of pulmonary nodules, the high contrast resolution between pulmonary nodules and lung parenchyma makes them ideal candidates for volumetric segmentation. More work needs to be done however to develop powerful segmentation methods ensuring precise and reproducible nodule segmentation (15).

Another important feature is that within the volume of a pulmonary nodule there is genomic heterogeneity which manifests as subtle differences within the nodules substance that cannot be readily appreciated by the naked eye. Nevertheless, this heterogeneity can be represented with radiomics, allowing for the statistical assessment of image datasets to produce diagnostic, predicative and prognostic models.

Finally, very substantial numbers of lung cancer datasets can be accessed via large inter-institutional databases such as the National Cancer Institute (NCI) Quantitative Imaging Network (QIN) as well as large trails like the National Lung Cancer Screening Trail (NLST). Sufficiently high powered statistical analysis of information extracted from these large cohorts is necessary for the extraction of useful quantitative imaging features.

Radiomic features in lung nodules and terminology

Pulmonary nodule radiomic features can vary considerably in complexity. At the most basic level automated radiomic features aim to replicate features traditionally captured by visual assessment by radiologists such as nodule size, shape and outline. Nodule histogram and texture analysis are more intricate forms of radiomics. A typical histogram analysis of a pulmonary nodule denotes the distribution of densities within the nodule. Entropy for example is a term that describes the randomness of discrete neighboring intensities within a greyscale image while skewness is a marker of the symmetry, or more precisely asymmetry, of a data-set around the sample mean.

More complex forms of texture analysis use mathematical equations to describe the relationship between neighbouring pixels and their distribution through the nodule. For example a widely used form of radiomics called wavelet analysis describes the concept of breaking imaging data down into different frequency components called wavelets and using this data to extract features relating to image texture and intensity.

While subjective correlates of histogram analyses are usually not possible to make with the naked eye, the concept of Hounsfield unit distribution within a region of interest is one that can be readily understood by most radiologists. Even some of the more complex forms of textural analysis which are less easy to understand, nevertheless do have visual descriptive correlates such as ‘coarseness’.

Once features have been extracted, the next process in radiomics is establishing relationships between patterns of features and clinical variables, also known as data mining. This can vary from straightforward statistical analyses based on a priori hypotheses, to machine learning methods. Machine learning is a field of computer science which combines the study of pattern recognition and computational learning theory to construct algorithms that can learn from data and make predictions on outcomes as well as uncover hidden insights. Random forests is an example of a machine learning algorithm which works by constructing a collection of decision trees.

Figure 1 illustrates the types of steps involved in the radiomic analysis of lung nodules

Clinical application of pulmonary nodule radiomics

Differentiating lung cancer from benign pulmonary nodules

Nodule size evaluation

In CT based lung cancer screening and incidentally detected indeterminate pulmonary nodules, a number of studies have shown that radiomics can improve the diagnostic accuracy

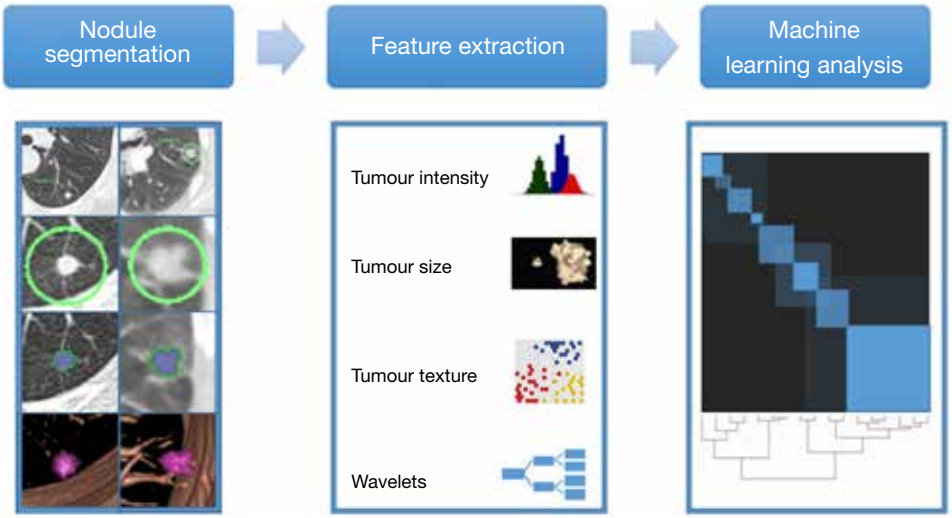

Figure 1 A summary of the steps involved in the process of radiomics. (I) Image acquisition and nodule volume segmentation; (II) extraction of features that quantifying nodule intensity, size, texture and wavelet texture; (III) feature analysis using machine learning techniques and the development of clinically predictive radiomic signatures.

to discriminate cancer from benign pulmonary nodules.

Nodule size can be more accurately and quantitatively assessed with the use of volumetry software than with manual caliper measurements. Nodule stability and growth rate can also be more confidently assessed by calculating a nodule's volume doubling time (VDT). Data from the NELSON lung cancer screening trial indicates that the likelihood of malignancy can be estimated according to VDT. For example, nodules with a VDT of <400 days have a chance of malignancy of 9.7% compared to 4.1% for VDTs between 400–600 days. Indeed, this basic form of radiomic nodule assessment has been integrated into the British Thoracic Society (BTS) guidelines for the initial assessment and surveillance of solitary pulmonary nodules (16).

Texture based analyses

A study by Ma *et al*. illustrated the potentially vast number of radiomic textural features that can be extracted from pulmonary nodules. The authors assessed 127 indeterminate pulmonary nodules and identified 583 features of nodule intensity, shape and heterogeneity. By analyzing these features they achieved 82.7% accuracy in classification of malignant primary lung nodules and benign nodules (17).

In another study, Hawkins *et al*. assembled two cohorts of 104 and 92 patients with screen-detected lung cancer matched with two cohorts of 208 and 196 screening subjects with benign pulmonary nodules. Image features were extracted from each nodule and used to predict the subsequent emergence of cancer. Twenty three stable features in a random forests classifier could predict nodules that would become cancerous 1 and 2 years hence with accuracies of 80% (area under the curve 0.83) and 79% (area under the curve 0.75), respectively (18).

Radiomic analysis has also been shown to have a role in evaluating subsolid nodules. Studies have identified textural features that are able to differentiate transient inflammatory nodules from malignant part-solid nodules, and also differentiate indolent adenocarcinoma in situ from invasive adenocarcinoma.

Lee *et al*. assessed textural features of 86 part-solid nodules. They found that low mean attenuation, lower 5-percentile CT number and higher positive skewness of attenuation were significant discriminators of transient from persistent part solid nodules. When texture analysis was used in combination with clinical and CT features differentiating power increased significantly when compared to clinical and CT features alone; the AUC rising from 79% to 92.9% (19).

In another study of 86 part-solid ground glass nodules Chae *et al*. successfully differentiated preinvasive lesions from invasive lung adenocarcinoma using a combination of texture based features (area under the curve, 0.981) with higher kurtosis and smaller mass being particularly good differentiators (20).

Histological sub-typing

There are a number of studies which have successfully demonstrated an association between radiomic features and NSCLC tumour histology (21,22)

Wu *et al*. extracted 440 radiomic features from segmented lung tumours on the pretreatment CTs of 350 patients. They observed that 53 radiomic features were significantly associated with tumor histology. By using a combination of wavelet based feature analysis tumour histological subtype could be reliably predicted (AUC 72%) (14).

One application (known as CANARY) has been specifically developed for the pathology evaluation of lung nodules. This radiomics tool has been shown to non-invasively risk stratify lung adenocarcinomas into aggressive (invasive adenocarcinoma) and more indolent forms (adenocarcinoma in situ and minimally invasive adenocarcinoma). Through the use of cluster analysis, CANARY aims to reduce the wide and complex pattern of voxel densities seen within pulmonary nodules down to nine representative so-called exemplars. These exemplars correspond to the predominant histopathology across the lung adenocarcinoma spectrum (23).

These results highlight the impressive long-term potential of non-invasive and cost effective radiomics tools for informing treatment choices and personalized therapy for lung cancer patients.

Gene expression-radiogenomics

There is emerging evidence that radiomics can be useful in the underlying gene expression profiling of NSCLCs and has been used to predict EGFR and KRAS mutation status in NSCLC. Currently the genetic subtyping of lung cancers often requires biopsy and re-biopsy of lung nodules often with multiple samples taken. The ability in the future to accurately predict genetic labels from CT offers the potential for enormous clinical benefit.

Liu *et al*. retrospectively evaluated the capability of CT-based radiomic features to predict epidermal growth factor receptor (EGFR) mutation status in 299 surgically-resected peripheral lung adenocarcinomas. Statistically significant differences were found in 11 radiomic features between EGFR mutant and wild type groups. They found that mutant EGFR status could be predicted by a set of 5 radiomic features (AUC 0.647). When radiomic features were added to a clinical model the predictive power increased significantly with the AUC increasing from 0.667 to 0.709 (P>0.0001) (24).

Another study has assessed the potential of textural analysis to differentiate K-ras mutant from pan-wildtype tumors, as well as it's prognostic potential by applying radiomics to 48 pre-treatment non-contrast CT studies with NSCLC. It was found that positive skewness with fine-texture and lower kurtosis with coarse-texture were significantly associated with K-ras mutations. They also demonstrated that quantitative CT textural analysis could accurately differentiate K-ras mutant from pan-wildtype tumors in 89.6% of cases and that Kurtosis was a significant predictor of overall survival and disease free survival, with a lower kurtosis value linked with poorer survival (25).

Prognostic indicators and disease response

In NSCLC, prognostic models have been developed for patients treated with surgery, radiotherapy or with targeted therapies. In each of these cases classifiers have been used to predict response and/or survival (26,27).

Coroller *et al*. examined whether pre-treatment radiomics data could predict pathological response after neoadjuvant therapy in patients with locally advanced NSCLC. In a cohort of 127 NSCLC patients they found 7 radiomic features were predictive for pathologic gross residual disease (AUC>0.6), and one for pathologic complete response (AUC=0.63). By contrast, no conventional imaging features were predictive. Tumors that did not respond well to neoadjuvant therapy were more likely to present a rounder shape and heterogeneous texture (28).

Other studies have shown that radiomic features extracted from CT images of lung cancers can be useful to distinguish radiation-induced fibrosis from tumor recurrence as well as identify patients with locally advanced lung adenocarcinoma at risk of developing distant metastasis (29).

A study performed by Mattonen *et al*. evaluated the accuracy of radiomics, for the predication of eventual local recurrence based on CT images acquired within 6 months of stereotactic ablative radiotherapy (SABR) in 45 patients with early stage NSCLC. A combination of five radiomic features demonstrated a AUC of 0.85 at 2–5 months post-SABR. At the same time point, three physicians assessed the majority of images as benign injury with overall errors of 34%~37%. These results suggest that radiomics can detect early changes associated with local recurrence which are not typically considered by clinicians. This could lead to a decision support system which could potentially allow for early salvage therapy of patients with local recurrence

following SABR (30).

Conclusions

The ever increasing number of indeterminate pulmonary nodules detected incidentally or during CT-based lung cancer screening provides considerable diagnostic and management challenges. It also however provides excellent opportunity for early stage characterization and tailored intervention and has enabled the development of a new field of research, namely radiomics. Radiomics also has the potential to revolutionize the diagnosis, surveillance and treatment planning of lung cancer allowing for personalized management in a way that is non-invasive and cost-effective.

Despite the initial evidence being promising more work needs to be done to improve the validity of these results before they can be applied in clinical practice. Foremost among the current challenges faced by radiomics in lung nodule assessment is the development of a universal language for CT descriptors, and harmonization of image acquisition parameters.

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Footnote

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From diagnosis to therapy in lung cancer: management of CT detected pulmonary nodules, a summary of the 2015 Chinese-German Lung Cancer Expert Panel

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Abstract: The first Chinese-German Lung Cancer Expert Panel was held in November 2015 one day after the 7th Chinese-German Lung Cancer Forum, Shanghai. The intention of the meeting was to discuss strategies for the diagnosis and treatment of lung cancer within the context of lung cancer screening. Improved risk classification criteria and novel imaging approaches for screening populations are highly required as more than half of lung cancer cases are false positive during the initial screening round if the National Lung Screening Trial (NLST) demographic criteria [≥30 pack years (PY) of cigarettes, age ≥55 years] are applied. Moreover, if the NLST criteria are applied to the Chinese population a high number of lung cancer patients are not diagnosed due to non-smoking related risk factors in China. The primary goal in the evaluation of pulmonary nodules (PN) is to determine whether they are malignant or benign. Volumetric based screening concepts such as investigated in the Dutch-Belgian randomized lung cancer screening trial (NELSON) seem to achieve higher specificity. Chest CT is the best imaging technique to identify the origin and location of the nodule since 20% of suspected PN found on chest X-ray turn out to be non-pulmonary lesions. Moreover, novel state-of-the-art CT systems can reduce the radiation dose for lung cancer screening acquisitions down to a level of 0.1 mSv with improved image quality to novel reconstruction techniques and thus reduce concerns related to chest CT as the primary screening technology. The aim of the first part of

this manuscript was to summarize the current status of novel diagnostic techniques used for lung cancer screening and minimally invasive treatment techniques for progressive PNs that were discussed during the first Chinese-German Lung Cancer. This part should serve as an educational part for the readership of the techniques that were discussed during the Expert Panel. The second part summarizes the consensus recommendations that were interdisciplinary discussed by the Expert Panel.

Keywords: Lung cancer; modern imaging; molecular markers; screening, minimally-invasive therapy; response assessment; pulmonary nodules (PN)

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Introduction

Outside of screening environments, the majority of lung cancer patients are still detected with advanced disease. The 5-year overall survival (OS) rate of this group of lung cancer patients is still poor despite various improvements in lung cancer therapy in the recent years. As a potential to substantially impact on the overall prognosis of lung cancer patients, recent data from lung cancer screening trials using low dose computed tomography (LDCT) clearly demonstrated a significant reduction of lung cancer related mortality mainly due to detection of lung cancer at earlier stages. Consequently, lung cancer screening with LDCT is now recommended in at risk populations in the United States. However, even though proven to be effective to reduce lung cancer mortality, LDCT as originally applied in NLST is hampered by a high rate of false positive findings, overdiagnosis and high costs. Moreover, improved risk classification criteria for non US or European screening populations are needed since approximately more than half of lung cancer cases are missed if NLST criteria [≥30 pack years (PY), age ≥55 years] are applied to the Chinese population mainly due to non-smoking related risk factors.

Screening

Since effective lung cancer screening requires repetitive CT scans usually on an annual basis radiation dose reduction is critical for screening applications to avoid the induction of screening related malignancies new state-of-the-art CT systems equipped with the latest dose reduction technologies including optimized iterative reconstruction algorithms as well as spectral shaping with dedicated filters allow high quality chest CT acquisitions with radiation dose levels around 0.1 mSv. Beside dose reduction, more effective screening is mainly dependent of the measurement techniques of pulmonary nodules (PN) as well as follow-up strategies. Within this context, volumetry based screening concepts such as investigated in the NELSON trial seem to achieve higher specificity compared to data as recently published in NLST.

Treatment of progressive PNs

For fifteen to twenty percent of stage T2 or T3N0M0 (<5 cm) non-small cell lung cancers (NSCLC) with or without pleural involvement, surgery remains the reference standard treatment. In case surgery is not possible, such as patients with poor pulmonary function, poor performance status, significant medical comorbidities, or patients' refusal of ordinary surgery, minimally-invasive therapy techniques like radiofrequency ablation (RFA), microwave ablation (MWA) of recently introduced irreversible electroporation (IRE) are more frequently considered in progressive PNs using screening as well as in patients with of oligo-metastatic disease, where the patient had progressive disease in some of the nodules, while the rest has successfully been treated by a systemic treatment.

Response assessment

Tumor response assessment in lung cancer patients undergoing targeted therapies, stereotactic body radiation therapy (SBRT) or non-surgical minimally invasive approaches require new strategies beyond RECIST and WHO criteria that are solely based on changes in tumor size. Yet a growing number of literature' suggests that the currently used objective criteria for progression may not always indicate clinical treatment failure and does not adequately determine disease biology, with the implication of potentially limiting their value in clinical trial analysis.

Therefore, these criteria represent pivotal determinants to the efficacy assessment for novel targeted therapies.

The motivation to organize this *German Chinese Lung Cancer Expert Panel* was the perception about an existing 'region gap' between German and China regarding different patient populations especially with respect to gender, smoking habit, and different environment influences. The *Expert Panel* entitled '*From diagnosis to therapy in lung cancer: Management of CT detective methods and pulmonary nodules*' was held on November 13–14, 2015, in Shanghai, China one day after the '*7th CGLCF 2015*'. The *Expert Panel* was divided into two main sessions. In the first educational part, invited imaging experts summarized the current scientific evidence on novel imaging techniques and the potential advantages and disadvantages for using these techniques in upcoming clinical trials and general clinical practice. In the second part, all invited multi-disciplinary experts discussed the value and the applicability of novel imaging and treatment techniques for various clinical scenarios. Accordingly, this article comprises two parts: a short review of the relevant subject areas followed by the recommendations of the Expert Panel.

Educational part

Lung cancer screening

Role of LDCT screening approaches

Driven by the well-known inverse relationship between stage and survival in lung cancer patients a variety of lung cancer screening and early detection approaches have been explored until today.

Opening new opportunities, the US National Lung Screening Trial (NLST) demonstrated for the first time a 20% reduction in lung cancer related mortality by screening for lung cancer using LDCT compared to chest X-ray. Screening population comprised of selected high risk individuals aged 50 and older and heavy ever smokers with more than 30 PY. The proven efficacy of the CT based screening approach prompted the US preventive services task force to recommend an annual lung screening program for high risk individuals effective from January 2015.

Despite the obvious success there may also be potential adverse outcomes in terms of high false positive rate, overdiagnosis (detection of cancer that would never have become symptomatic), bias and cost-effectiveness concerns. Following the recommendation of the Fleischner Society, all noncalcified nodules measuring at least 4 mm in any diameter were considered positive in NLST resulting ultimately in more 95% false positive cases. This triggered a controversial discussion about the potential harms of lung cancer screening and resulted in several suggestions to improve specificity such as increasing the threshold of positivity to 6 mm in diameter. Beside changes in unidimensional diameter other approaches such volumetry based lung cancer screening concepts are currently under clinical research, particular in Europe.

First reports from the NELSON lung cancer screening trial using volumetric nodule measurements yielded high specificity and sensitivity, with only a small number of interval cancers. The results of this study could be used to improve screening algorithms, and reduce the number of missed cancers. Small nodules (those with a volume <100 mm^3 or diameter <5 mm) are not predictive for lung cancer. Immediate diagnostic evaluation is necessary for large nodules (≥300 mm^3 or ≥10 mm). Volume doubling time assessment is advocated only for intermediate-sized nodules (with a volume ranging between 100–300 mm^3 or diameter of 5–10 mm). Nodule management protocols based on these thresholds performed better than the simulated ACCP nodule protocol (1). Overall, the diagnostic strategy in NELSON trial led to considerably less false-positive referrals compared to other lung cancer screening trials, with very high negative predictive values found in the first and second screening rounds. Mortality results are still pending, but the knowledge already gained in the NELSON trial and its side-studies provide valuable information in the field of screening for lung cancer (1,2).

Based on currently applied rigid inclusion criteria for lung cancer screening in the United States, it is estimated that up to 50% of all lung cancer cases will be missed (3). This clearly indicates an urgent need for improved selection criteria to possibility extend screening to additional segments at risk of the entire population.

Beside the need for a higher specificity of screening approaches an improved CT hardware with reduced radiation dose is of outmost importance. Dose reduction matters, particular if repeated CTs are performed like in lung cancer screening (4). Several lines of evidence indicate that radiation doses for CT imaging lead to increased cancer risk, even at higher age. For example the BEIR VII (Biological Effects of Ionizing Radiation) assumes a linear no threshold correlation between radiation dose and cancer risk in medical imaging. This issue has been rigorously addressed by several radiation dose reduction advances in CT scanner technology (5). Haubenreiser *et al.*

prospectively investigated image quality and radiation dose of 100 kVp spectral shaping chest CT using a dedicated tin filter on a 3rd generation dual-source CT (DSCT) in comparison to standard 100 kVp chest CT (6). The results of this study demonstrate that 100 kVp spectral shaping chest CT allows 90% dose reduction when compared to 100 kVp chest CT without spectral shaping.

Summary

- Lung cancer screening with LDCT is effective to significantly reduce lung cancer mortality but is still hampered by a high rate of false positive findings, overdiagnosis and not neglecting costs;
- Improved risk classification criteria for screening populations are needed as more than half of lung cancer cases are missed if NLST criteria (≥30 PY, age ≥55 years) are applied;
- Radiation dose reduction is crucial for screening applications. New generation CT systems work with radiation doses down to 0.1 mSv for LDCT of the chest and are helpful tools in screening;
- Volumetric based screening concepts such as investigated in the NELSON trial seem to achieve higher specificity.

Role of biomarkers

Early detection of lung cancer can be achieved by analysis of biomarkers from tissue samples within the respiratory tract such as sputum, saliva, nasal/bronchial airway epithelial cells and exhaled breath condensate or through peripheral biofluids such as blood, serum and urine (7). Autofluorescence bronchoscopy has been employed in research setting to identify pre-invasive lesions not identified on CT scan. Although most of these modalities are not yet commercially available in clinic setting, they will be available in the near future and clinicians who care for patients with lung cancer should be aware. As non-invasive screening test causing no discomfort to participants the use of volatile organic compounds as biomarker for lung cancer has been subject to intensive research within the last years. As reported by Fu *et al.*, the concentrations of 2-butanone, 2-hydroxyacetaldehyde, 3-hydroxy-2-butanone, and 4-hydroxyhexenal (4-HHE) in the exhaled breath of lung cancer patients (n=97) were significantly higher than in the exhaled breath of healthy smoker and nonsmoker controls (n=88) and patients with benign PNs (n=32). The concentration of 2-butanone in exhaled breath of patients (n=51) with stages II though IV NSCLC was significantly higher than in exhaled breath of patients with stage I (n=34). The carbonyl and volatile organic compounds profile in exhaled breath determined using this new silicon microreactor technology provides for the noninvasive detection of lung cancer (8,9).

Exhaled breath analysis in lung cancer patients reaches in small to midsized discovery trials sensitivities and specificities up to ≥90%. However large scale trials in a true screening environment are still missing.

Gas chromatography with mass spectroscopy is currently the most widely used technique but new sensor technology will allow the development of point of care testing. Once more broadly available and standardized, the combination of exhaled breath testing with imaging in terms of an integrated screening approach seems a promising expansion strategy of screening to reach a broader population. Albeit lung cancer is the current research & development focus further malignancies but also inflammatory diseases such as COPD or Asthma are candidates (10).

Summary

Novel biomarkers could aid in early detection and refine risk classification of individuals within screening programs. Volatile organic compounds have significant potential for early cancer detection. However, large scale clinical trials in a true screening setting are still missing.

Minimally-invasive therapy in lung cancer

The method of percutaneous ablation essentially incorporates two methods: thermal and non-thermal therapy. RFA has been established as an effective and often used thermal therapy for treatment of primary lung cancer. MWA as an alternative to RFA, has some principal advantages for lung ablation, such as less severe heat sink effect and a faster and higher heating.

Beland *et al.* reported in 2010 that 57% of the patients under RFA have a median disease-free survival of 23 months (11). This was confirmed by Lanuti *et al.* analyzing long-term results of RFA for inoperable early-stage lung cancers (12). Mean maximum diameter of the 38 treated tumors was 2.0±1.0 cm (range, 0.8–4.4 cm). Median OS was 30 months and 2- and 4-year survival rates were 78% and 47%, respectively.

Bi *et al.* compared the effectiveness of RFA with SBRT in inoperable stage I NSCLC (13). The local control rate (LCR) for SBRT is significantly higher than that for RFA; 3-year LCR was 55% *vs.* 88%, though OS is not different between the two groups.

A phase II study performed by Higuchi *et al.* confirmed the effectiveness of RFA for unresectable primary and secondary thoracic malignancies. [18F]Fluorodeoxyglucose

(FDG)-PET analysis, 3–6 months after ablation, is a useful tool to assess LCR (14). Percutaneous ablation of small cell lung cancer (SCLC) and NSCLC has been demonstrated to be both, feasible and safe in nonsurgical candidates. RFA, the most commonly used technique for ablation, has a reported rate of complete ablation of ~90%, with best results obtained in tumors <2 to 3 cm in diameter. The best reported 1-, 3-, and 5-year OS rates after RFA of NSCLC are 97.7%, 72.9%, and 55.7%, respectively. Since RFA in NSCLC is a method used often for the unfit, in most studies cancer-specific survival is greater than OS due to severe comorbidities in patients. Aside from tumor size and stage, these comorbidities are predictors for survival (15).

To summarize recent publications on RFA of NSCLC: the indication includes mostly 1–2 lesions of <2 cm in diameter; slow growing disease; there is no detection of recurrence possible with standard CT before 6 months follow-up (16) and by PET after 3 months (17); frequently false positive lymph nodes (LN) after RFA (reaction to treatment, disappear after 6 months, also possible for needle tract).

MWA versus RFA

Today, MWA is a standard and routine ablation method for inoperable tumors. The reason is that the extent of MWA zones was not significantly different among completely different tissues, such as liver, adipose tissues, and muscles (18). MWA with ≥5 minutes' time duration can induce coagulation zones with clinical relevant shape. However, future clinical studies are still required to determine the role of MWA in different tissues. MWA create larger ablations than RFA if controlled for power in *ex vivo* tissue. For RFA complete ablation was in 78%~96% in tumors <2 cm, but however, in tumors >2 cm there was seen a shorter PFS and a high recurrence rate. Using MWA has the advantage that if the tumor <5 cm, complete ablation resulted in 95% of patients (18-21).

Planché *et al.* (*Cardiovascular and Interventional Radiology* 2013) found that larger tumor size and the use of an internally cooled electrode were independent risk factors for local progression after RFA of lung tumors. In a recent paper it was shown that MWA has less heat sink effect: in models a single MWA antenna can create ablation zones large enough to cover lung tumor of <4 cm diameter with no heat sink effect for vessels up to 6 mm (22). In clinical practice the advantage of the method MWA lies in faster reaching therapeutic temperatures, applicable higher temperatures, and faster ablation.

But MWA also has some possible complications as pneumothorax, hematoma, bronchopleural fistula, missed ablation of the needle track, injury of different structures, bronchi, pericardium vessels (skin burn) among others.

A paper published in *Translational Lung Cancer Research* showed similar effect of lobectomy or sub lobar resection in comparison to SBRT, RFA, and MWA (23). Thus, if patients cannot benefit from surgery, then RFA and MWA can be an alternative treatment choice. Still these new treatments have not enough support in evidence by clinical trials; hence, their optimal role has not yet been determined. Treatment recommendations should be given at an individualized level, based primarily on the size and location of the tumor, the patient's age, comorbidities, and performance status, and the strength of the available evidence.

IRE

IRE as described by Neumann in 1982 is based on short, pulsed electric fields and can increase permeability of cell membrane. The theory of "pore formation" can be described as electroporation (24). Applications of electroporation were used first for water sterilization for industrial use to eliminate microorganisms. It is now being used as IRE for tumor therapy (25,26). The advantages of IRE for tumor ablation comprises the following facts: non-thermal, short, pulsed electric fields; nanometer-sized pores in phospholipid layer; disturbance of homoeostasis; induction of apoptosis; tissue selectivity, no thermal damage (which means extracellular matrix/fibrous structures remain intact as bile ducts, vascular structures, renal pelvis); sharp ablation margins; no heat sink effects; "short ablation times" (minutes); and peri-interventional delineation [CT, ultrasound, magnetic resonance imaging (MRI)]. Disadvantages of IRE are small ablation areas; use of multiple needles; muscle contractions caused by direct excitation of motor end plate, which will often apply general anesthesia for relaxation; and cardiac arrhythmias can happen also. There are no long term results and no randomized studies yet available. IRE had shown some beneficial survival data in the treatment of pancreatic tumors (27).

Technical obstacles using IRE in lung cancer are the facts that electrodes may be have closed contact to surrounding solid tissue and in comparison with the target tissue showing relative homogenous conductivity. The main reason why IRE is challenging in lung is that air filled pulmonary alveoli are a strong isolator. So a phase II trial on lung malignancies did not show a survival benefit using IRE. But it should notice that patient selection may encumber better result for IRE treatment (28).

Functional imaging for response assessment to targeted therapies in lung cancer

Tumor response assessment in patients undergoing targeted therapies requires new strategies beyond RECIST and WHO criteria, which always used size to evaluate response. Although Herbst *et al.* found 65% stable disease (SD) and 20% partial remission (PR) in erlotinib plus bevacizumab treated group, anti-angiogenetic drug can cause central necrosis and cavitation, which suggested that size is a poor criterion for response (29). Yet a growing number of literature suggests that our current objective criteria for progression may not always indicate treatment failure and do not adequately capture disease biology, potentially limiting their value in clinical trial analysis (30). Thus, they proposed for upcoming trials a "personalized' tumor response assessment by applying cancer- and therapy-specific criteria to correct pitfalls of conventional criteria (31). Therefore, these criteria represent a critically important contribution to the assessment of efficacy by novel targeted therapies, allowing the radiology community to be part of personalized cancer care in the era of molecular medicine. Response patterns in different treatment scenarios are various, such as chemotherapy, anti-angiogenetic therapy and immunotherapy.

Thus, Zhao *et al.* found that compared with the uni- and bi-dimensional techniques, semi-automated tumor segmentation enables the identification of a larger number of patients with absolute changes in tumor volume of at least 20% and 30% (32). Volumetric measurements more accurately predict PR in patients with lung cancer. However, inter-observer reproducibility of semi-automatic tumor diameter measurement and volumetric analysis in patients with lung cancer exist, by using computer-assisted size assessment in primary lung tumor, inter-observer variability can be reduced to about half to one-third compared to standard manual measurements (33). Hence, Lee *et al.* evaluated new response criteria in patients treated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) compared with RECIST, and proposed new criteria for a more accurate response assessment in patients with NSCLC undergoing EGFR-TKI therapy (34). In this study, a decrease of tumor attenuation in Hounsfield units was an accurate marker of therapy response even in tumors with a less than 30% decrease in maximum size. The decrease in tumor attenuation was caused by the high incidence of tumor cavitation after EGFR-TKI therapy as a surrogate of central tumor necrosis. This sign of therapy response was not observed in patients undergoing standard chemotherapy. By applying these criteria, patients classified as responders showed a higher median OS (18.4 months) than patients with poor response (8.5 months). In contrast, RECIST criteria were negative in 16 patients that achieved response according to the new criteria (35).

Early FDG PET-CT after the start of erlotinib treatment identified patients who benefited from this targeted therapy (36). Thirty-four patients with untreated stage IV NSCLC were evaluated in this phase II trial. Changes in FDG and FLT uptake after 1 (early) and 6 (late) weeks of erlotinib treatment were compared with non-progression measured by computed tomography after 6 weeks of treatment, progression-free survival (PFS), and OS. Results showed early FDG-PET predicts PFS, OS, and non-progression after 6 weeks of therapy with erlotinib in unselected, previously untreated patients with advanced NSCLC independent from *EGFR* mutational status (37). PET-CT detected early recurrence in 24% of patients after radical radiotherapy with or without chemotherapy. 3% of recurrences were detected in asymptomatic patients who underwent potential curative treatment (38).

Dynamic contrast-enhanced CT (DCE-CT): volume perfusion CT

Tumor angiogenesis leads to an increase of regional blood flow (BF) and blood volume (BV) and, thereby, contrast-enhancement of lung cancer tissue. Tumor perfusion and therapy-induced perfusion changes can be quantified by DCE-CT, i.e., it can assess tumor density at different times, based on consecutive CT scans that are acquired after the injection of contrast material. The technique provides quantitative data of tumor BF, BV, permeability, and the mean transit time (MTT) of iodinated contrast material through the tumor. NSCLC with higher perfusion is more sensitive to chemo-radiation therapy than that with lower perfusion (39). After chemo-radiation therapy, findings at perfusion CT can act as a significant predictor of early tumor response and OS among NSCLC patients. CT-perfusion can adequately evaluate therapy-induced alterations in NSCLC, and perfusion parameters correlate with therapy response assessment performed with RECIST criteria (40). Evaluating perfusion parameters, CT-perfusion can demonstrate therapy-induced changes in patients with different types of lung cancer and identify response to treatment with excellent agreement to RECIST measurements. Their results showed that some therapy-induced changes could be anticipated on the basis of CT-perfusion parameters of the lesions at baseline examinations. In particular, baseline values of BF, BV and time to progression (TTP) were different among PR,

PD and SD patients.

Dual-energy CT (DECT)

DECT is selective iodine quantification as a marker of tumor BV. Kim *et al.* evaluated tumor responses to anti-angiogenic therapy and compared with the baseline CT results using both RECIST (size changes only) and Choi's criteria (reflecting net tumor enhancement). They found DECT may serve as a useful tool for response evaluation after anti-angiogenic treatment in NSCLC patients by providing information on the net enhancement of target lesions without obtaining non-enhanced images (41). To investigate the correlation between maximum standardized uptake value (SUVmax) of FDG PET-CT and iodine-related attenuation (IRA) of DECT of primary tumors and FDG PET-CT positive thoracic LN in patients with lung cancer. A strong correlation was found in patients with study intervals ≤21 days (n=17; r=0.768; P=0.017). Analysis of histological subtypes of lung cancer showed a strong correlation between SUVmax and maximum IRA in the analysis of all patients with NSCLC (r=0.785; P=0.001) and in patients with NSCLC and study intervals ≤21 days (r=0.876; P=0.024). DECT could serve as a valuable functional imaging test for patients with NSCLC as the IRA of DECT correlates with SUVmax of FDG PET-CT (42).

Thus, DECT seems to be an attractive and cost-effective method to monitor response to treatment in patients undergoing anti-angiogenic therapies although one has to acknowledge that based on the currently available evidence, the technique is still not "ready for prime time" to replace RECIST of WHO criteria in prospective clinical trials.

Diffusion weighted MRI (DW-MRI)

DW-MRI is a tool for the accurate staging of mediastinal LN and the evaluation of tumor response during therapy. DW-MRI visualizes the microscopic movement of water molecules within tissues and has been proposed for the differentiation between benign and malignant LN's. In metastatic LN's, diffusion is limited due to the obstruction of LN by tumor cells. Therefore, metastatic LN's have significantly lower apparent diffusion coefficient (ADC) values than those of the benign LN's. Nomori *et al.* directly compared the accuracy of DWI-MRI and FDG PET-CT for determining nodule category in patients with NSCLC and compared the results of both modalities to those, of histopathological examination (43). Among 734 analyzed LN stations, histopathology revealed 36 metastatic and 698 non-metastatic LN's. There was no significant difference between DW-MRI and FDG PET-CT in the detection of metastatic LN stations. However, DW-MRI was more accurate than FDG PET-CT in the identification of non-metastatic LN stations because of the lower rate of false-positive results (43,44).

Expert Panel Consensus (EPC)

EPC: general comments

After the summary of diagnosis and management of CT detected size progressive PNs, it became clear that there is a need for interdisciplinary interaction on imaging and treatment due to the given region gap between China and Germany in clinically useful measures and required radiology research, as well as among clinicians about the ongoing developments and opportunities in imaging. All participants agreed that the communication between radiologists and clinicians has to be improved in terms of quantity and quality. Moreover, the communication between Germany and China on ongoing developments and their potential applications in clinical trials should be formalized and accelerated. There was also a general consensus about the requirement for more integrative access of Chinese and German lung cancer specialists for the planning of clinical trials. This should ensure that the most appropriate imaging methods are applied and will be further validated in upcoming clinical trials investigating targeted therapies.

Overall, it was considered essential that in the era of molecular oncology the radiology and oncology community should get more actively involved in clinical trials and patient care.

EPC: lung cancer screening

The US NLST demonstrated a 20% reduction in lung cancer mortality and a 6.7% decrease in all-cause mortality. The NLST is the only trial showing positive results in a high-risk population, such as in patients with old age and in heavy (ever) smokers. Lung cancer screening using a low-dose chest CT might be beneficial for the high-risk group. However, there may also be potential of adverse outcomes in terms of high false positive rates, over diagnoses, bias and cost-effectiveness. Based on currently applied rigid inclusion criteria for lung cancer screening up to 50% of all cases will be missed. There is a need for higher specificity of screening and an improved CT hardware with a reduced radiation dose. Also, there is an urgent need to improved selection criteria

and the possibility for an extension of screening population. Dose reduction matters, particular if repeated CTs are performed like in lung cancer screening. Typical radiation doses for CT imaging lead to increased cancer risk, even at a higher age. Obviously a correlation between radiation dose and cancer risk is seen Radiation dose reduction by advances in CT scanner technology is mandatory. Nensa *et al.* posted on ECR 2013 have shown that with different CT devices, such as Gated-helix or flash-helix, a dose reduction for CT coronary angiograms of about 90% can be realized.

EPC

PET-CT, dynamic contrast enhanced CT as well as DECT might be useful tools to better characterize detected solitary PN's. Further research is necessary to define thresholds and standardize procedures. Novel biomarkers could aid in early detection and refine risk classification of individuals within screening programs. Volatile organic compounds have significant potential for early cancer detection. However, large scale clinical trials in a real screening setting are still warranted. The panel also suggests considering the difference between China and Germany, in terms of different smoking habits, occupational exposures, infections, driver gene mutation rates, and gender. High risk of non-smoker lung cancer: the panel discussed that there is no current evidence that would support an ideal risk population. However, there is consensus that the screening population in China is different due to the air and indoor pollution, and different EGFR mutation rates. Thus, the panel encourages studies which will investigate concurrent specific population for China. The following questions should be addressed: 'Can we promote screening combined with smoking cession? What is the status of Germany or China?' The panel is aware of the fact that there is an increasing number of female smokers seen nowadays in lung cancer. The panel also suggests being careful about smoking cessation program, as more and more non-smokers were detected to be lung cancer patients.

EPC: PNs

CT is an important tool in the evaluation of solitary and multiple PN. There is a wide variety of PN's, which represents a diagnostic challenge. The primary goal in the evaluation of these nodules is to determine whether they are malignant or benign. Chest CT is the best imaging technique to identify the origin and location of the nodule as 20% of 'nodules' found on chest X-ray turn out to be non-pulmonary when imaged with another technique.

EPC

CT scans of 1 mm images are important to show the PNs. Most small solid nodules found incidentally in lung cancer screening are intrapulmonary LN's. Further development of new technologies and improvement of currently available methods of less and noninvasive methods of diagnosis are the key components of the never-ending process of refinement of our ability to accurately determine the etiology of LN's.

Future research is required to study the role of biological and biochemical markers in the diagnosis of small LN's, as well as to determine potential new therapeutic strategies for malignant LN's, such as therapies targeting signal pathways, angiogenesis, immunotherapy, and cryotherapy.

EPC: DCE-CT

Tumor angiogenesis leads to an increase of regional BF and BV and, thereby, contrast enhancement of lung cancer tissue. Tumor perfusion and therapy-induced perfusion changes can be quantified by DCE-CT. DCE-CT can assess tumor density at different times, based on consecutive CT scans that are acquired after the injection of contrast material. The technique provides quantitative data of tumor BF, BV, permeability, and MTT of iodinated contrast material through the tumor. NSCLC with higher perfusion is more sensitive to chemo-radiation therapy than that with lower perfusion. After chemo-radiation therapy, findings at perfusion CT are a significant predictor of early tumor response and OS among patients with NSCLC. CT-perfusion can adequately evaluate therapy induced alterations in NSCLC, and perfusion parameters correlate with therapy response assessment performed with RECIST criteria.

Recommendations

Evaluating perfusion parameters, CT-perfusion can demonstrate therapy-induced changes in patients with different types of lung cancer and identify response to treatment with excellent agreement to RECIST measurements.

EPC: DECT

DECT is selective for iodine quantification as a marker of tumor BV. Yoo Na Kim *et al.* evaluated tumor responses to anti-angiogenic therapy and compared with the baseline CT results using both RECIST (size changes only) and Choi's criteria (reflecting net tumor enhancement). They found

DECT may serve as a useful tool for response evaluation after anti-angiogenic treatment in NSCLC patients by providing information on the net enhancement of target lesions without obtaining non-enhanced images. To investigate the correlation between SUVmax of FDG PET-CT and IRA of DECT of primary tumors and FDG PET-CT positive thoracic LN's in patients with lung cancer. A strong correlation was found in patients with study intervals ≤21 days (n=17; r=0.768; P=0.017). Analysis of histological subtypes of lung cancer showed a strong correlation between SUVmax and maximum IRA in the analysis of all patients with NSCLC (r=0.785; P=0.001) and in patients with NSCLC and study intervals ≤21 days (r=0.876; P=0.024). DECT could serve as a valuable functional imaging test for patients with NSCLC as the IRA of DECT correlates with SUVmax of FDG PET-CT.

EPC

DCE-CT seems to be an attractive and cost-effective method to monitor response to treatment in patients undergoing anti-angiogenic therapies although one has to acknowledge, that based on the currently available evidence, the technique is still not "ready for prime time" to replace RECIST of WHO criteria in prospective clinical trials.

EPC: DW-MRI

DW-MRI is a tool for accurate staging of mediastinal LNs and the evaluation of tumor response during therapy. DW-MRI visualizes the microscopic movement of water molecules within tissues and has been proposed for the differentiation between benign and malignant LN's. In metastatic LN's, diffusion is limited due to the obstruction of LN's by tumor cells. Therefore, metastatic LN's have significantly lower ADC values than that of the benign LN's. Nomori *et al.* directly compared the accuracy of DWI-MRI and FDG PET-CT for determining nodule category in patients with NSCLC and compared the results of both modalities to those, of histopathological examination. Among 734 analyzed LN stations, histopathology revealed 36 metastatic and 698 non-metastatic LN's. There was no significant difference between DW-MRI and FDG PET-CT in the detection of metastatic LN stations.

EPC

DW-MRI was more accurate than FDG PET-CT in the identification of non-metastatic LN stations because of the lower rate of false-positive results.

Can we improve of lung cancer screening by an integrated (biomarker plus imaging) approach?

Rational lines at refine selection of high risk patients for LDCT screening to increase pre-test probability, and better preselection would ultimately allow the expansion of screening programs beyond groups matching NLST criteria. Test requirements should be as follows: Sufficient high statistical power; ready availability; ease of use; non-invasive with high acceptance rate; cost-effectiveness. Exhaled breath analysis in lung cancer patients reaches in small to midsized discovery trials sensitivities and specificities up to ≥90%. Large scale trials in a real screening environment are still missing. Gas chromatography with mass spectroscopy is currently the most widely used technique. New sensor technology will allow the development of point of care testing. Combination of exhaled breath testing with imaging in terms of an integrated screening approach is promising. Albeit lung cancer is the current research and development focus further malignancies but also inflammatory diseases such as COPD or Asthma are candidates.

EPC

It is recommended that data of a large patient number should be collected. With reduction in lung cancer related mortality of 20% LDCT lung cancer screening (NLST) proved its effectiveness but is compromised by a high rate of false positives, over diagnoses and costs. Improved risk classification criteria for screening populations are needed as more than half of lung cancer cases are missed if NLST criteria (≥30 PY, age ≥55 years) are applied. There is a need for higher specificity of screening and improved CT hardware with reduced doses. Therefore, advanced methods for effectively perform lung cancer screening are clinically needed.

EPC: RFA

RFA has been increasingly reported in the literature as an effective therapy for treatment of primary lung cancer. RFA is becoming an accepted treatment for primary NSCLC in patients who are not candidates for sub-segmental resection or lobectomy. The role of RFA and other percutaneous ablative therapies has still to be established, either as a stand-alone therapy or in combination with other modalities such as radiation therapy. RFA is safe and feasible for the treatment of unresectable stage I lung cancer. Limitations of this technology for solid tumor ablation in the lung

are tumor size and proximity to blood vessels. The major advantages of RFA therapy for the treatment of medically unresectable stage I NSCLC are low morbidity, single application, reduced hospital stay, and well-defined zones of tissue destruction. In contrast, conventional radiotherapy and stereotactic radiotherapy require multiple treatments and are often associated with pneumonitis, bronchial stenosis, esophagitis, and complications of fiducial markers.

EPC

It was agreed in the discussion that whenever possible, RFA should be implemented in those NSCLC patients where surgery and SBRT cannot be tolerated in case of 1–2 lesions, size <2 cm, and slow growing disease. There is no detection of recurrence possible with standard CT before 6 months follow-up, by PET after 3 months, to identify frequently false positive relapse after RFA. However, caution is warranted due to the relatively limited number of RFA studies.

EPC: RFA versus MWA

A thermal ablation technique in which microwave energy is used provides all of the benefits of RFA and some substantial advantages. Preliminary work in this field shows that MWA may be effective for treating solid neoplasms in the lung. Possible benefits of MVA include consistently higher intra-tumor temperatures, an improved convection profile, the capability of using multiple applicators, larger tumor ablation volumes, and no need for grounding pads. However, there is no known literature for lung tumor RFA using these devices. Microwave technology allows multiple applicator techniques to be used during a single ablation treatment, each powered by an individual microwave generator.

EPC

RFA can be used to treat small, localized tumor, which keep distance to structures at risk, and have a promising results in 2 years OS with lesions <2 cm. MWA technique is less effected by heat sink, and can be used at larger tumors than with RFA, but is not yet common in applied studies.

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Footnote

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How to diagnose pulmonary nodules: from screening to therapy

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Lung cancer is still the leading cause of cancer-related death worldwide and early detection allows for a better survival for lung cancer, which is supported by the results of the National Lung Screening Trial (NLST) in 2011 (1). Early screening by low-dose computed tomography (LDCT) in high-risk patients can induce a 20% reduction in lung cancer-specific mortality, therefore LDCT is now recommended for lung cancer screening. It is demonstrated that the implementation of early screening could increase the number of detected pulmonary nodules by an estimated 875,000 per year (2). However, it is suggested that the majority of screen detected nodules were benign, making it necessary to establish a comprehensive criterion of screening, diagnosis and therapy of pulmonary nodules so that lung cancer can be early detected and not over-diagnosed.

Screening

As we know that a pulmonary nodule is identified as a focal rounded or irregular opacity in the lung, can be well or poorly defined, measures less than 30 mm, and surrounded by aerated lung and is not associated with atelectasis or lymph node enlargement (1,3).

The current evaluation criteria of nodules are mainly divided according to the opacity and diameter of the nodules, and the patients are identified as low-risk and high-risk according to the age, smoking history, former tumor history, etc. (4). The recommendation of screening is differed on the solid and sub-solid nodules, and as a special part of sub-solid nodules, ground-glass nodules (GGN) are listed as a separate category, since it is demonstrated that the ground-glass opacity (GGO) has a more possibility of histology of adenocarcinoma, and Claudia I. Henschke *et al.* found in their recent research that a part-solid or nonsolid nodule is more likely to be malignant than a solid one, even when nodule size is taken into account (5,6).

In 2016, the Fleischner Society pulmonary nodule recommendations are still using the cutoff value of diameter in solid nodules as 4, 4–6, >6–8 and >8 mm, since nodule <4 mm is proved to have a low probability of malignant disease (7). The cutoff value of diameter sub-solid nodule is set as 5 mm in the statement from the Fleischner Society and if solitary pure GGNs ≤5 mm, no CT follow-up require and multiple pure GGNs ≤5 mm should obtain follow-up CT at 2 and 4 years. Initial follow-up CT at 3 months is needed and recommended to confirm persistence. If persistent, dominant nodules with part-solid or solid component are suggested to be biopsied or surgical resected, especially for lesions with >5 mm solid component (8).

Diagnosis

During the follow-up, there are several nodule features presented in the CT image may give the evidence that the nodule could be malignant and the iconic features are margin, size, growth and the presence and the distribution of calcification (5,9).

Recent studies suggest some new aspects of the nodule features helping to diagnose a malignant nodule. Another famous lung cancer screening trial—Dutch-Belgian randomised lung cancer multi-slice screening (NELSON) trial first reported to using the volumetric measurements as a remarkable nodule since it yielded high specificity and sensitivity, a nodule with a volume <100 mm^3 is not predictive for lung cancer and the volume doubling time assessment is recommended for the nodules with a volume

ranging between 100–300 mm^3 (10). The British Thoracic Society guidelines for the investigation and management of pulmonary nodules published in 2015 also take the volume as the characteristic of nodule (8,11). As a result, dynamic contrast-enhanced CT (DCE-CT) is demonstrated to be a useful screening method besides LDCT (12).

When the features suggesting the malignance of the nodule are detected, the diagnostic approaches will then be approved. In clinic, the diagnostic approaches are divided as non-invasive and invasive methods. As the most common non-invasive method using in clinic, fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT was considered to have limited value in nodule <8 mm, especially in pure GGN (11). However, recent studies have rebuilt the diagnostic value of ^{18}F-FDG PET/CT for evaluation of solitary pulmonary nodules. A latest meta-analysis suggested that although current evidence showed moderate accuracy, PET/CT is still a useful method for detecting malignant pulmonary nodules qualitatively (13).

Besides the surgery, the invasive diagnostic method is percutaneous lung biopsy and bronchoscopy. Endobronchial ultrasonography with guide sheath (EBUS-GS), electromagnetic navigation bronchoscopy (ENB) and virtual bronchoscopic navigation (VBN) are the up-to-date technologies in the interventional pulmonology (14). The combination of these methods has been proven to have precisely diagnostic value for pulmonary nodules, especially for GGNs.

Therapy

When the malignance of the nodule is confirmed or highly suspected, surgery is recommended depending on number of the nodules and the fitness of the individual. Lobectomy or anatomical segmentectomy is the treatment of choice (2).

Non-surgical recommended treatments are stereotactic ablative radiotherapy (SABR) and radiofrequency ablation (RFA). As an effective therapy, RFA has been increasingly reported for the treatment of primary lung cancer and becomes an accepted treatment for primary non-small cell lung cancer (NSCLC) in patients who are not candidates for surgery. SABR is proved to revolutionize radiation therapy for early stage lung cancer in the literature, having the advances in imaging and highly conformal and accurate radiation delivery and can achieve tumor control rates compared with surgery.

Conclusions

"*The best way to predict the future is to invent it*." The combination of early detection strategies and innovative therapies can give patients more confidence, aim to find earlier cancer, give optimal treatment, and make life better.

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Footnote

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Transthoracic needle aspiration in solitary pulmonary nodule

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Abstract: With improved awareness of public health and the recent advances in various imaging technologies, the detection rate of solitary pulmonary nodules (SPN) is continuously increasing. Transthoracic needle aspiration (TTNA) has represented a major approach for the diagnosis and differential diagnosis of pulmonary masses, owing to its simplicity and minimal invasiveness. This paper demonstrates the role of TTNA in SPN.

Keywords: Transthoracic needle aspiration (TTNA); solitary pulmonary nodule (SPN); lung cancer; diagnostic tool

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Introduction

Lung cancer remains the leading cause of cancer deaths worldwide. With the established role of computed tomography (CT) screening for lung cancer, and the broad application of high-resolution CT, the solitary pulmonary nodule (SPN) are increasingly detected. Accurate assessment, proper treatment and timely surgical resection of malignant pulmonary nodules will be highly beneficial to the survival of patients with lung cancer (1). Therefore, the discovery rate of SPN is evidently elevated: most of them are benign, but some of them are lung cancer. The diagnosis of this kind of nodules is difficult and obtaining tissue samples to conduct pathology examination is the key point. The main ways to obtain a specimen for pathology diagnosis include exfoliative cell examination of sputum, bronchoscopy, transthoracic needle aspiration (TTNA), video-assisted thoracic surgery (VATS) and open-lung biopsy. The exfoliative cell examination of sputum is easy and non-invasive, but its positive rate is low. VATS and open-lung biopsy must be conducted under general anaesthesia, with risk, surgical trauma and high cost; nevertheless, some patients cannot undergo general anaesthesia. Bronchoscopy has a great diagnosis value in central type lung nodules, but the determination value in peripheral SPN is limited. TTNA, as a minimally invasive diagnostic method, has been widely used in the diagnosis of small nodules. In 1976, Haaga and Alfidi (2) reported the first case of CT-guided pulmonary puncture biopsy, and after that, this technology has been continuously developing and updating. By reviewing the latest literature, we summarized the relevant notes and strategies about TTNA in SPN diagnosis.

TTNA as diagnostic tool

Currently, an accepted definition of SPN is a single, well circumscribed, radiographic opacity <30 mm in diameter surrounded by aerated lung and not associated with atelectasis, hilar enlargement, or pleural effusion (3). SPN can be caused by a variety of factors, including malignant

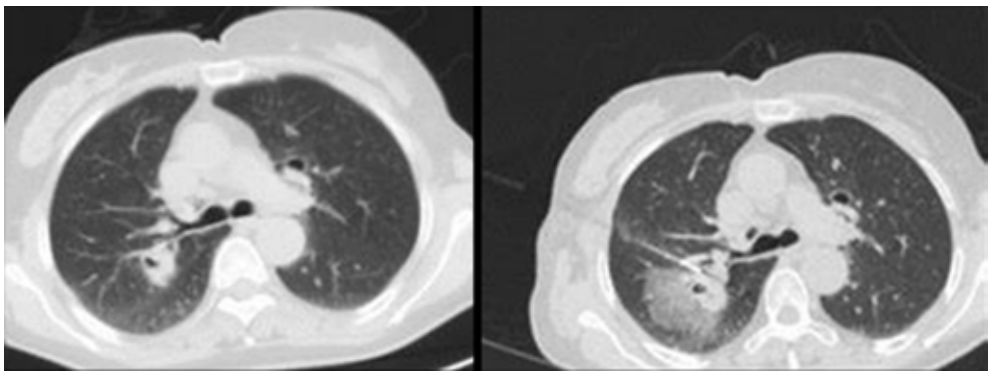

Figure 1 It shows the solitary pulmonary nodule (SPN) adherent to a major pulmonary artery and within a few mm of right lower lobe bronchus carrying the risk of pulmonary haemorrhage, pneumothorax, and development of a fistula. Extra-care and planning are needed when lesions lie very close to major vessels; an example is shown where the lesion was biopsied safely. These lesions are biopsied with computed tomography (CT) scan guidance.

diseases, or a range of benign lesions. In recent years, an important type of pulmonary nodules has gradually increased, namely the subcentimeter nodules, which refer to those with a diameter <8 mm. Studies have shown that sub-centimeter lung nodules have an overall low degree of malignancy (4). Improved imaging techniques such as high-resolution chest CT scan, result in the most common identification of small and often sub-centimetric SPN (5). With high-resolution CT, lung nodules can be categorized in a more accurate and detailed way. Ground-glass opacity (GGO) is a particular type of pulmonary nodules: is a sign of slightly increased density on the CT where the bronchial and vascular textures are still visible (1). Although most SPN is benign, the pathology of the nodule is crucial to a patient with a history of cancer even if the SPN is small and peripheral. Also, even in small pulmonary lesions <1 cm, the overall malignancy rate is as high as, or slightly lower than that in nodules >1 cm (5). TTNA is a minimally invasive diagnostic method, with a high positive diagnostic rate, less injury and low cost; so, it has been widely used in the routine diagnosis of SPN. Diagnosis of TTNA on small nodules has the following features:

(I) Wide adaptation range. Except for central type lesions, the diagnostic rate of bronchoscopy on the peripheral type and diffuse lesions is little while TTNA can be applied both in central type lesions or peripheral type and diffuse lesions, as long as there is no apparent adhesion in blood vessels (*Figure 1*). It is vital that other SPN mimics are excluded on imaging alone, and invasive procedures avoided (*Figure 2A*,*B*);

(II) TTNA has a high accuracy. CT scan can clearly show the location, density of pulmonary nodules and anatomic relationship between lesions and the surround tissues, and it can also locate the puncture site, the angle and the depth accurately. For lesions about 0.5–1 cm, it can also successfully conduct biopsy under CT guidance. It is important to emphases: (I) extrinsic/thoracic wall lesions can mimic an SPN; (II) malignant SPN can increase as well as reduce in size; (III) benign lesions may co-exist; (IV) some lesions with a wider differential such as BAC almost always need tissue sampling; (V) not all calcified lesions are benign (*Figures 2-8*);

(III) High diagnostic accuracy. TTNA is a well-established, useful procedure. However, the diagnostic accuracy of TTNA depends on the size and location of the lesion, as well as the guidance technique, and decreases from over 90% to 25% when the malignant nodule is small (<1 cm), and to 70% when the lesion is benign. As many as 29% of patients whose conditions were not diagnosed as malignant on trans-thoracic needle biopsy were ultimately found to have carcinoma (5). According to literature reports, the sensitivity and specificity of lung biopsy are separately 86% and 98.8% while its sensitivity and specificity can reach 91%, 94% by combining with perspective and CT guidance (7,8). The accuracy of puncture is evidently related to the location, depth and size of lesions; for nodules <2 cm, the total diagnosis accuracy of CT-guided puncture is about 77.2% (9); while for

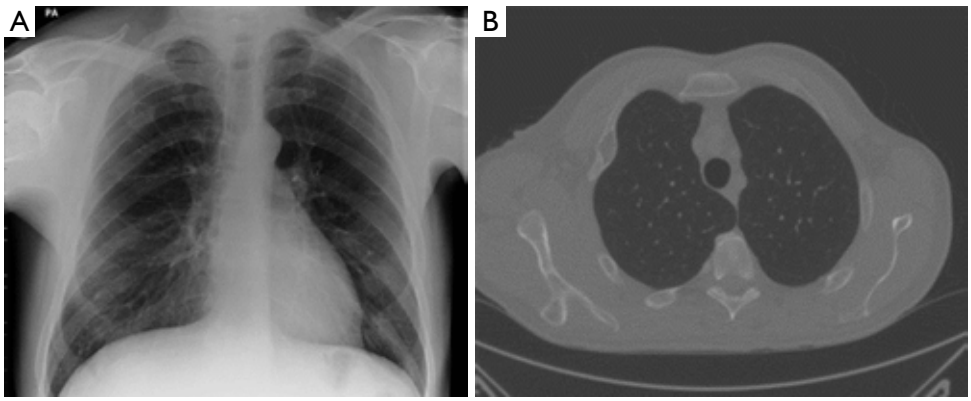

Figure 2 The SPN should be confirmed before invasive procedures. (A) It is vital that extrinsic lesions, such rib lesions simulating a solitary pulmonary nodule (SPN) are identified and dealt with on imaging alone. The roentgenogram shows a bone lesion in the right upper zone, confirmed by an axial computed tomography (CT)-scan (*Figure 2B*); (B) an axial CT scan on the same patient as in *Figure 2A*, showing an expansible lesion within a rib; as the patient was asymptomatic with normal blood parameters, the consensus was to follow the lesion with a roentgenogram. The lesion remains stable and asymptomatic after 3-year follow-up.

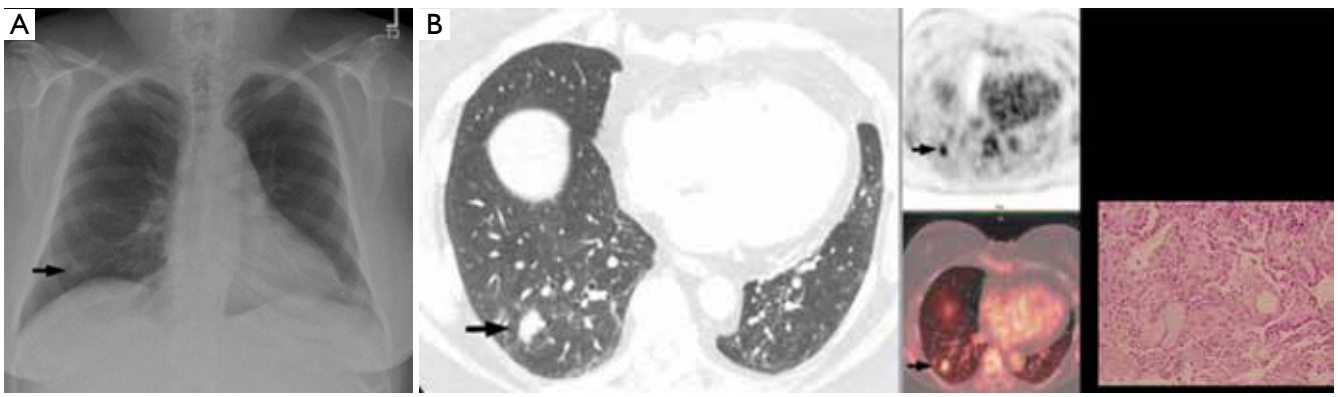

Figure 3 Solitary pulmonary nodule (SPN) should be genuine before embarking on an invasive pathway. (A) It is important to determine as to whether an SPN is genuine before embarking on an invasive pathway. In the example shown a nipple shadow was queried, although the shadow is rather high for a nipple; (B) the SPN seen in *Figure 3A* was biopsied, with histological findings that of bronchiolitis obliterans organizing pneumonia (BOOP). The SPN was FDG-PET avid, which has the potential for misdiagnosis.

nodules with the diameter about 0.5–0.7 cm, its sensitivity is only 50%. At the same time, a number of aspirates also seriously influence the diagnosis of lesion nature; for nodules with the diameter <1 cm, only 77% lesion sampling can satisfy the pathology diagnosis (10); according to reports by Tsukada *et al*., the diagnosis accuracy of diameter 6–10, 11–20, 21–30 mm are separately 66.7%, 78.9% and 86.7% (11);

(IV) High safety. Although TTNA is a safe and reliable examination method, it is still a traumatic investigation, so there are still some complications. The main complications of TTNA mainly include pneumothorax and haemorrhage. According to literature reports, the incidence of pneumothorax is about 10%~40% while the incidence of pulmonary injury is about 26%~33% (12). The occurrences of these complications are not only related to nodule size, depth to the chest wall and patients' basal lung function, but also related to the preoperative preparation, operation technology and patients' cooperation.

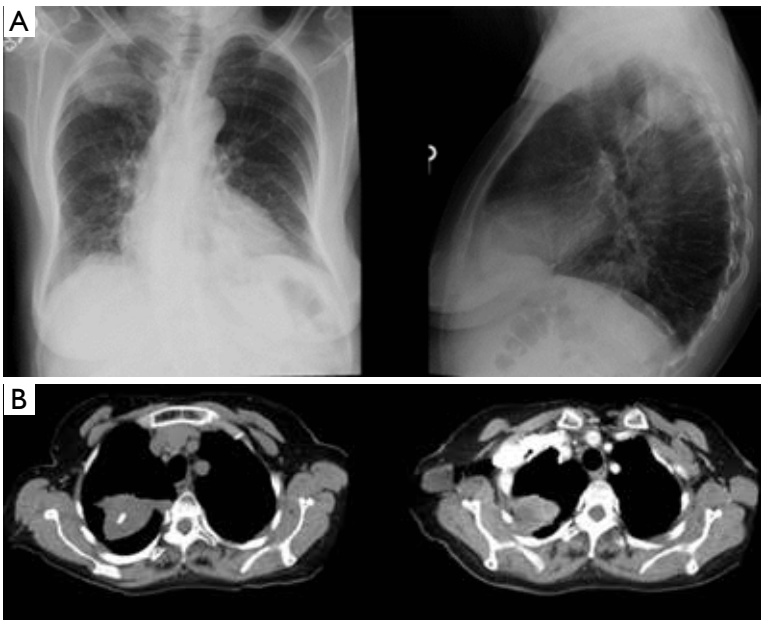

Figure 4 Characteristics of the scar carcinoma. (A) A posterior-anterior and lateral chest radiogram show calcification in a right apical solitary pulmonary nodule (SPN), proved scar carcinoma [see computed tomography (CT) scan]. Calcification with an SPN does not exclude malignant nodules (6); (B) the SPN evident on the CXR (*Figure 4A*), which in spite of the internal tumour calcification the lesion was malignant with areas of tumour necrosis and invasion of the chest wall, representing a scar carcinoma.

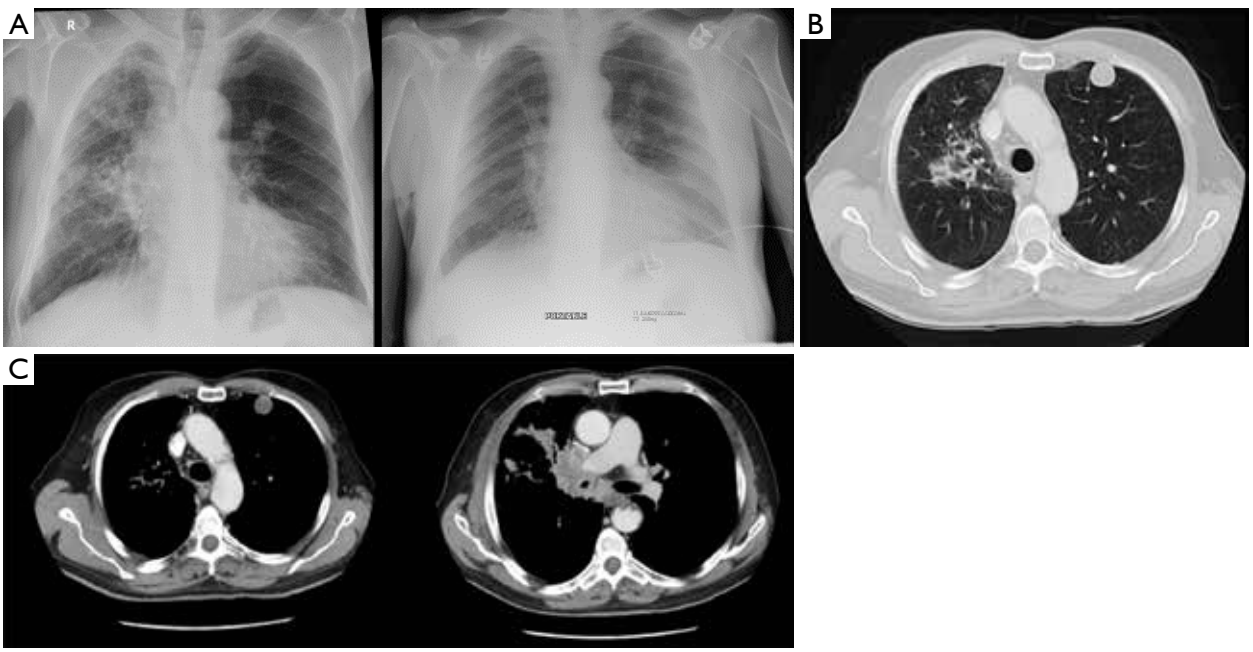

Figure 5 Emphases are made that benign and malignant tumours may coexist creating difficulty in staging the disease. (A) Emphases are made that benign and malignant tumours may coexist creating difficulty in staging the disease. In the case shown a benign chondroid hamartoma (left lung) & bronchogenic carcinoma (right lung) co-exist; (B) emphases are made that benign and malignant tumours may coexist creating difficulty in staging the disease. In the case shown a benign chondroid hamartoma (left lung) & bronchogenic carcinoma (right lung) co-exist; (C) emphases are made that benign and malignant tumours may coexist creating difficulty in staging the disease. In the case shown a benign chondroid hamartoma (left lung) & bronchogenic carcinoma (right lung) co-exist.

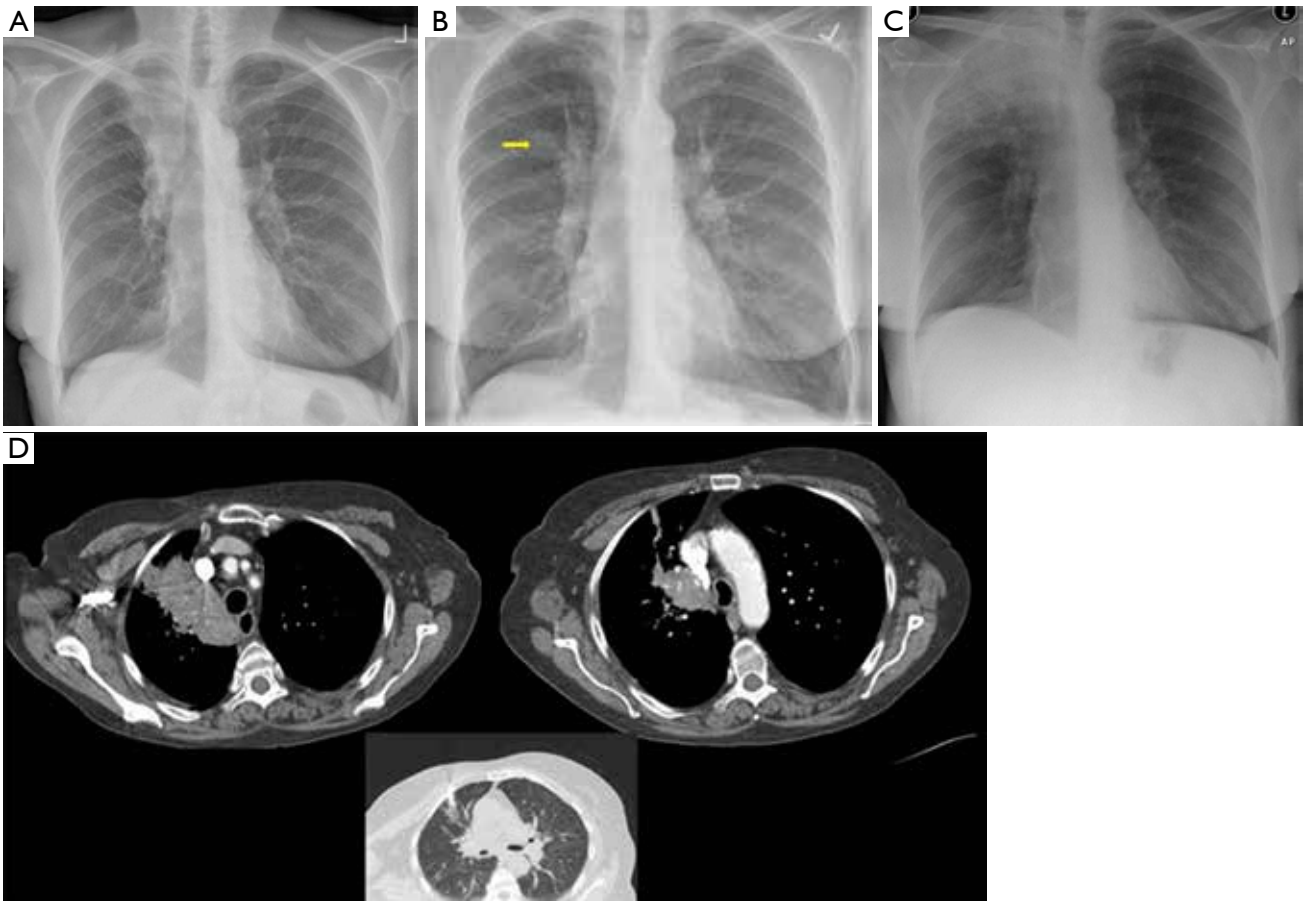

Figure 6 Dynamic follow-up is an important method for confirming the character of the solitary pulmonary nodule (SPN). (A) An SPN can grow as well as reduce in size; it is important to make sure there is no associated infection or bronchial obstruction from a mucous plug. A roentgenogram of a 53-year-old shows a classical right upper atelectasis. The patient was a non-smoker. The patient had a cough with raised inflammatory markers. The patient was treated with a *cephalosporin* for 2 weeks; (B) a repeat radiograph of the same patient as in *Figure 6A* taken 3 weeks later show considerable resolution of the right upper lobe atelectasis. However, a mass remains evident in the right upper lobe (arrow); (C) a chest X-ray taken 3 months later of the same patient as in *Figure 6A,B* show the right upper lobe opacity has shown a significant increase in size; (D) axial contrast-enhanced computed tomography (CT) scans at the level of the aortic arch show a solid tumour with a comet tail sign. A CT guided needle biopsy revealed an adenocarcinoma.

Tips and pitfalls

The direct purpose of TTNA is to improve the diagnosis accuracy of nodules. Before the procedure, patients' clinical and imaging materials should be fully understood. If it is an enhanced scanning, sites with evident enhancement should be chosen for puncture. If it is a benign tumour, a puncture needle with larger diameter should be selected to obtain enough pathology tissue. If it is tuberculosis, polymerase chain reaction-tuberculosis DNA (PCR-TB DNA) and acid-fast bacillus examination should be conducted on aspirates. CT characteristics of the focal localization scanning should be analyzed seriously. If there is any larger lesion, sites with evident enlargement should be chosen as the puncture targets and liquefactive necrosis tissue should be avoided. If a Franseen needle is selected, movement at the time of negative suction and cutting should be softly and each puncture time should be shortened as shorter as possible to reduce the influence of focal haemorrhage on obtaining the final samples. To maintain a certain amount of negative pressure, the selection of syringes is also critical. If the syringe volume is too small, it is not sufficient to

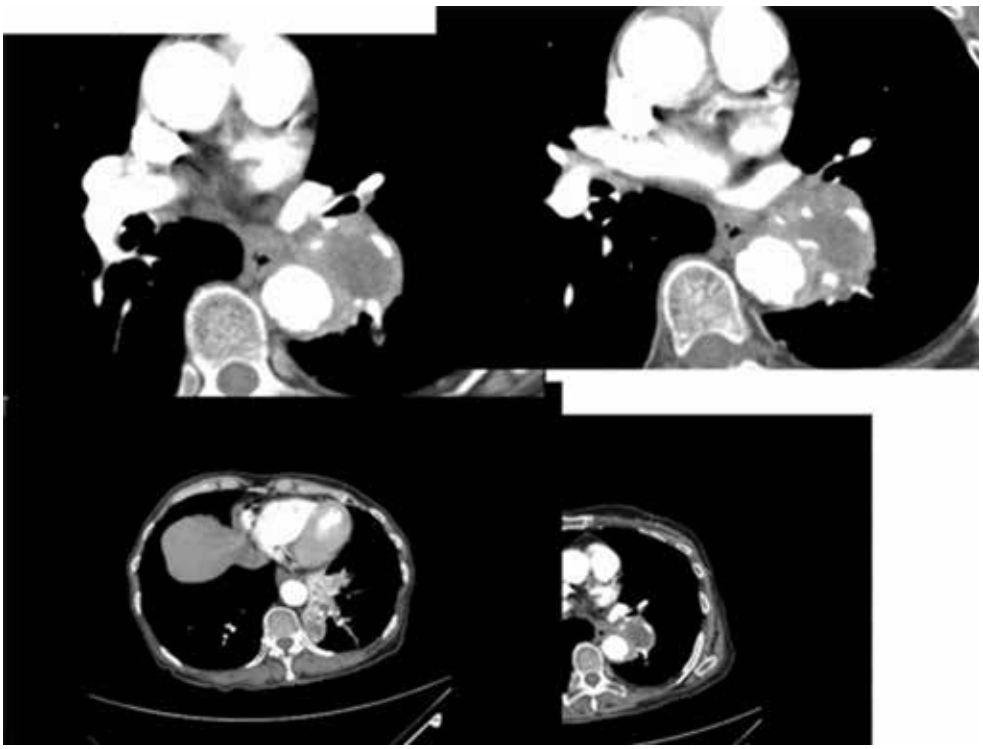

Figure 7 The importance of identifying vascular anomalies cannot be over emphasized to prevent embarkation on invasive procedures. A 53-year-old man presented with left-side pleuritic chest pain and shortness of breath. He gave a history of DVT-3 months earlier and was on oral anticoagulants. A CTPA was performed for suspected pulmonary embolism. An anomalous vessel was shown in the left para-aortic space. Multiplanar reconstruction showed this vessel arising from the left pulmonary artery and drained into the left brachiocephalic vein. The findings suggested an incidental anomalous pulmonary venous drainage. No pulmonary embolus was identified.

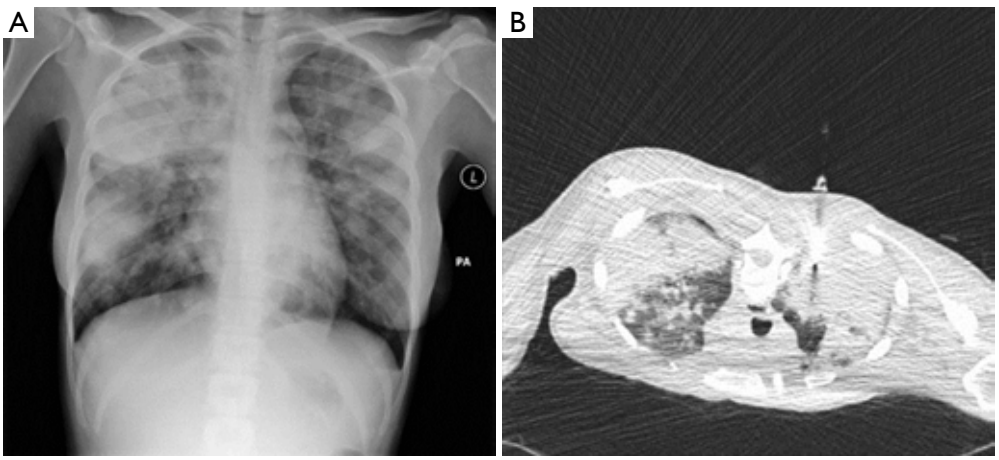

Figure 8 Transthoracic needle aspiration (TTNA) in bronchoalveolar carcinoma (BAC). (A) The diagnosis of BAC can be problematic as BAC can mimic many other pathologies and tissue diagnosis is often required; (B) the diagnosis of BAC can be problematic as BAC can mimic many other pathologies and tissue diagnosis is often required. Accurate needle placement, as shown above, is necessary.

produce a proper negative pressure effect, but if it is too large, it will be difficult to operate, so syringes of 10 or 20 mL will be a right choice. After pulling out the needle, samples should be carefully searched and selected, especially when there is plenty of sludge blood in the aspirates. If the operator is a lack of experience, he/she should conduct the selection, film preparation, submission and deciding whether there should be another puncture with the assistance of a pathology physician or a clinical physician. Therefore, the operator's experience is paramount. The extension-type automated biopsy gun should be selected because one puncture can keep several materials, which will make treatment available for several times. This set of puncture equipment is expensive, while Franseen needle is cheaper and its repeat utilization rate is high. Besides, for patients with blood in the sputum after operation or patients with a highly suspected malignant tumour or those who are not satisfying with the puncture results, Sputum cytology examination should be conducted after the process. Since biopsy may quickly make cancer cells fall off and flow out along the bronchi, so the positive rate of post-operative cytological examination of sputum is often higher. The skills of core biopsy, combination use, and aspiration in our present cohort were higher than those reported by Yamagami *et al*. (13). Differences in lesion characteristics (the length of aerated lung or the proportion of experienced operators) may affect diagnostic accuracy. The number of specimens and biopsy methods are significantly different between success or failure groups. Hiraki *et al*. reported that the acquisition of a larger number of samples significantly increases diagnostic accuracy because the sampling error decreases (14). However, the rate of pneumothorax in patients with a single puncture is significantly less than in patients with three tentatives. With the coaxial technique, core biopsy could be performed without other pleural punctures and with a reduction of the risk of pneumothorax. A higher rate of complications was reported using the more approaches compared with a single technique in a study by Klein *et al*. (15). While simultaneously considering the risks and benefits, it is important to decide first the number of specimens and to choose the right method. Regarding the methods, the diagnostic accuracies of aspiration, core biopsy, and the combination of techniques were respectively 93.4%, 95.2%, and 100.0%. Yamagami *et al*. investigated the efficacy of the combination use of core biopsy and aspiration compared with each method alone (13). Lung biopsy is needed to determine the particular cell type of lung cancer. Moreover, the current trend of using receptor antagonists as chemotherapeutic agents requires more tissue to determine the presence of specific receptors and perform various kinds of immunohistochemical staining. Also, when a lesion is shown to be benign, clarification of the particular cell type may be necessary. Core biopsy or a combination of core biopsy and TTNA is required for higher diagnostic accuracy and more pathologic information. It is not obvious whether the consistency of the nodule is a significant factor associated with diagnostic accuracy. Hur *et al*. reported that the diagnostic accuracy of aspiration is significantly lower for evaluating pure GGO nodules than mixed GGO nodules (16). On the other hand, the sensitivity, the specificity, and the accuracy of TTNA were not significantly different between pure GGO nodules and mixed GGO nodules according to Yamauchi *et al*. (17). Considering that a diagnosis of adenocarcinoma made up most of the false-negative biopsy results, adenocarcinomas presenting as pure GGO nodules may also show low diagnostic yield on TTNA (18). Within the past decade, new techniques have emerged that offer guidance through the tracheobronchial tree during bronchoscopy to help reach and biopsy the nodule, such as electromagnetic navigation bronchoscopy (ENB) and endobronchial ultrasonography (EBUS) (*Figure 9*) (19,20). The diagnostic accuracy of peripheral pulmonary nodule by EBUS and ENB is 46–86.2% (21-23), and 62.5–76.9% respectively (24,25). Steinfort *et al*. (26) comprehensively analyzed 1,420 EBUS biopsies of the peripheral pulmonary tumour from 16 studies, with a sensitivity of 0.73 ($P<0.05$, 95% CI: 0.70–0.76). Also, a meta-analysis of 15 studies involving 1,033 patients with SPN by Gex *et al*. (27) showed that diagnostic accuracy of pulmonary nodules with ENB was 73.9% ($P<0.05$, 95% CI: 68.0–79.2). Based on the above data, we suggest that the diagnostic accuracy of SPN with TTNA is significantly higher than that with EBUS or ENB. Therefore, the positive predictive factors of TTNA of pulmonary nodules are correlated to nodule size (the larger the diameter, the better the accuracy), non-calcific density (the higher the density, the better the accuracy), and distance between the nodule and the pleural plane (the shorter the distance, the better the accuracy). The most common negative predictive factor of TTNA is the wrong placement of the needle tip, not appreciated in the native axial images but retrospectively observed in the sagittal and axial oblique CT images. The diagnostic accuracy of cytologically assisted TTNA can, therefore, be improved by the use of imaging, which is useful to plan the needle path while performing needle aspiration (28).

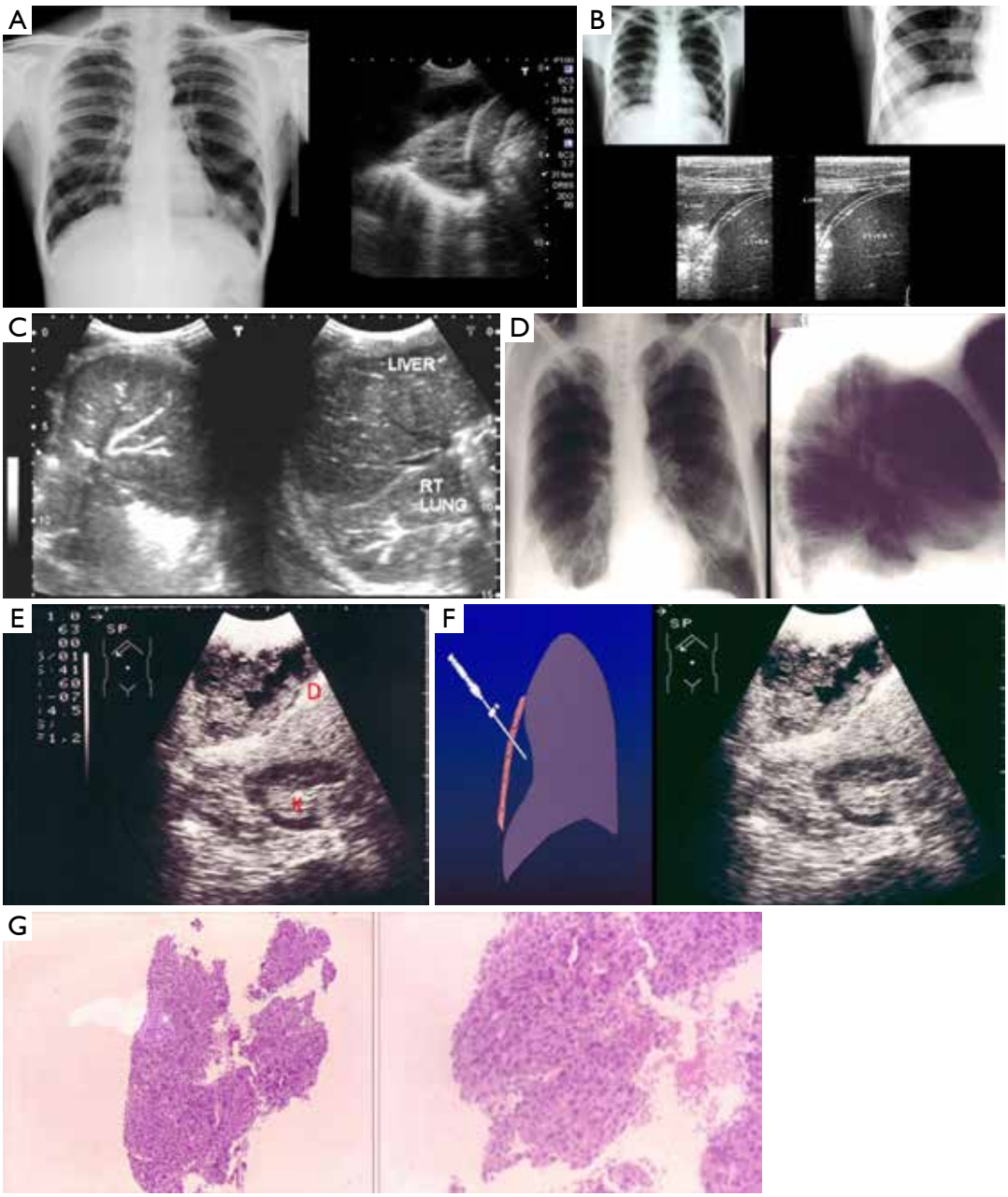

Figure 9 Electromagnetic navigation bronchoscopy (ENB) and endobronchial ultrasonography (EBUS) in the diagnosis for solitary pulmonary nodule (SPN). (A) Ultrasound is a non-invasive, reliable and cheap modality that can characterize lung nodules, particularly peripheral lesions. More central lesions can be analyzed by navigational bronchoscopy. SPN/mass at the left cardio-phrenic angle is shown to represent lung consolidation with a pleural effusion above the left hemidiaphragm. Note the air bronchogram (bright echoes)/fluid within the bronchi (anechoic); (B) an opacity right costophrenic angle show lung consolidation (hepatization). The lesions mimic a Hampton's hump Courtesy Ravi Kadasne Consultant Radiologist Al Ain UAE; (C) ultrasound shows an air-bronchogram at the right lung base in an area of lung consolidation; (D) a roentgenogram of a 52-year-old smoker with a history of asbestos exposure presented with a cough for 6 months. It's hard to be certain from the CXR as to whether there is consolidation or a pleural effusion at the left lung base; (E) an ultrasound shows a solid mass above the inverted diaphragm (D). There are areas of necrosis within the mass. The right kidney is marked K; (F) the lesion was biopsied under ultrasound guidance, and core tissue was taken; (G) histopathological slides of the core tissue obtained by ultrasound-guided core biopsy. (left H & E ×100, right H & E ×400).

Conclusions

Selecting the appropriate diagnosis method according to the clinical features of SPN patients can maximally improve the diagnostic accuracy and avoid adverse reactions. For TTNA, the risk of pneumothorax increases if the nodule is near the hilar or away from the surface, or the puncture path passes pulmonary bulla, or when the patient's lung function is compromised. The risk of haemorrhage is high in a biopsy if the nodule is located near large blood vessels, such that other diagnostic methods should be considered in this case. Overall, TTNA has several advantages such as high diagnostic rate, low cost, and manageable adverse reactions. With proficient operating skills and precise positioning of puncture, the diagnostic accuracy of TTNA can be significantly improved, and its complications can be minimized. Thus, this conventional method is still useful if it is the appropriate approach based on the SPN features. The development of new technology will add more complementary values to the traditional ones.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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^{18}F-FDG-PET/CT in the assessment of pulmonary solitary nodules: comparison of different analysis methods and risk variables in the prediction of malignancy

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Objective: To compare the diagnostic performance of different metabolical, morphological and clinical criteria for correct presurgical classification of the solitary pulmonary nodule (SPN).

Methods: Fifty-five patients, with SPN were retrospectively analyzed. All patients underwent preoperative ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT). Maximum diameter in CT, maximum standard uptake value (SUV_{max}), histopathologic result, age, smoking history and gender were obtained. Different criteria were established to classify a SPN as malignant: (I) visually detectable metabolism, (II) SUV_{max} >2.5 regardless of SPN diameter, (III) SUV_{max} threshold depending of SPN diameter, and (IV) ratio SUV_{max}/diameter greater than 1. For each criterion, statistical diagnostic parameters were obtained. Receiver operating characteristic (ROC) analysis was performed to select the best diagnostic SUV_{max} and SUV_{max}/diameter cutoff. Additionally, a predictive model of malignancy of the SPN was derived by multivariate logistic regression.

Results: Fifteen SPN (27.3%) were benign and 40 (72.7%) malignant. The mean values ± standard deviation (SD) of SPN diameter and SUV_{max} were 1.93±0.57 cm and 3.93±2.67 respectively. Sensitivity (Se) and specificity (Sp) of the different diagnostic criteria were (I): 97.5% and 13.1%; (II) 67.5% and 53.3%; (III) 70% and 53.3%; and (IV) 85% and 33.3%, respectively. The SUV_{max} cut-off value with the best diagnostic performance was 1.95 (Se: 80%; Sp: 53.3%). The predictive model had a Se of 87.5% and Sp of 46.7%. The SUV_{max} was independent variables to predict malignancy.

Conclusions: The assessment by semiquantitative methods did not improve the Se of visual analysis. The limited Sp was independent on the method used. However, the predictive model combining SUV_{max} and age was the best diagnostic approach.

Keywords: Positron emission tomography (PET); solitary pulmonary nodule (SPN); diagnostic accuracy; clinical variables; metabolic criteria

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Introduction

A solitary pulmonary nodule (SPN) is defined radiologically as an intraparenchymal lung lesion of less than 3 cm in diameter, with no associated atelectasis or adenopathy (1,2). The management of SPN is clinically controversial and is mainly dependent on the perceived probability of malignancy (3). The prevalence of lung cancer in patients with SPN varies widely, from 2%~13% in screening studies, to 46%~82% in positron emission tomography (PET)

studies (4,5). For a suspicious malignant SPN, percutaneous transthoracic biopsy, transbronchial needle aspiration biopsy or video-assisted thoracoscopic surgery provides histological information. However, these are invasive procedures, skill-dependent and with variable accuracy to the diagnosis of cancer (6-8).

PET with ^{18}F-fluorodeoxyglucose (FDG) has had an important impact to the diagnosis of benign and malignant nodules. Some reports have suggested that PET can reduce the number of patients with pulmonary nodules who undergo unnecessary surgical biopsy (9). Therefore PET using ^{18}F-FDG is an accurate and noninvasive method for diagnosing SPNs, with an overall sensitivity (Se) of 95% and a specificity (Sp) of 82% (10). However, surgical resection is still needed to differentiate lung cancer from benign lesions in a significant number of cases (6). The combination of computed tomography (CT) and PET in the hybrid imaging, has showed an excellent performance in classifying SPN as benign or malignant, where the Se of CT and the Sp of PET, result in an overall significantly improved accuracy (3,11).

To determine the management and treatment of the patient with a SPN, is necessary to estimate the probability of malignity from clinical and imaging data. Some independent predictors of malignancy include age, current or past smoking history, previous extrathoracic malignancy, nodule diameter, spiculation, and upper lobe location (8,12). Although specific models exist for the calculation of the probability of malignancy of a SPN, they do not have enough accuracy to replace of the clinician's judgment. On the other hand, adding metabolic parameter derived from PET studies has showed to improve the prediction of malignancy in SPN (11,13), however, it is necessary to increase the evidence that support the use of such metabolic parameters.

FDG uptake on PET has been qualitatively and semiquantitatively evaluated. Visual assessment is usually based upon comparison of FDG lesion uptake with normal mediastinal blood pool (14) and is the simplest among all the analyses, but nodules with similar FDG uptake to the mediastinum are difficult to evaluate visually. In order to have a more objective assessment, a cut-off the maximum standard uptake value (SUV_{max}) has been used for the establishment of malignancy. However, a great number of factors can affect the SUV, among them, body size, the blood glucose concentration, the time after injection, and the lesion diameter (15). As a result, the SUV_{max} of a SPN could not reflect its true nature.

In an attempt to improve the diagnostic accuracy of the presurgical evaluation of the SPN, the integration of risk variables into predictive models has been carried out, because, contrary to the clinical judgment, quantitative predictive models might have advantages in accuracy and reproducibility (8,12-14,16). Even though, several CT derived parameters have been included in such predictive model, metabolic variables have been no included.

The purposes of the present study were as follows: (I) to determine an optimum semiquantitative criterion that allows discriminating between malignant and benign nodules and comparing with the visual assessment and (II) to derivate a model to estimate the pretest probability of malignancy of a patient with SPN based on clinical and PET/CT image variables.

Materials and methods

A retrospective evaluation of PET/CT image data, final pathological classification and risk clinical and demographic variables of patients with SPN was performed. The data analysis was carried out after the approval by the Institutional Review Board.

Patients

Between January 2007 and December 2012, patients with a suspicious SPN, underwent a combined whole-body FDG PET/CT imaging and surgical resection of the SPN were included. After surgery, a final histological diagnose was assigned.

Other patient's characteristics as gender, age and previous or current history of smoking were analyzed.

PET/CT image acquisition and interpretation

Patients fasted for at least 4 h and had blood glucose levels less than 160 mg/dL previous to an intravenous administration of 370 MBq of ^{18}F-FDG.

FDG PET/CT scans were performed approximately 60 min after FDG administration using an integrated PET/CT scanner (Discovery STE 16, GE Healthcare). PET/CT was obtained from the head to proximal thighs. Prior to PET acquisition, helical CT was performed to provide attenuation correction, with acquisition parameters for the CT of 120 kV and modulated 120 mA. No oral or intravenous contrast agents were used. Emission images were acquired in three-dimensional (3D) mode, 3 min per

table position. PET images were reconstructed using CT for attenuation correction with ordered-subset expectation maximization iterative reconstruction algorithm. The PET and CT section thickness was 3.8 mm.

Two experienced nuclear medicine physicians reviewed the FDG-PET/CT studies in consensus. In the visual analysis of the PET data, a lesion was defined as negative (no FDG uptake visually detected) or positive (FDG-avid SPN regardless of its intensity).

For semiquantitative analysis, a circular region of interest was placed over the nodule location with the peak activity. The maximum intensity of FDG uptake was defined by body-weight SUV_{max} measurement using the commercially available software provided by the manufacturer. On the other hand, the nodule diameter (mm) was assessed in axial projection on CT image.

Four metabolic criteria were used to consider a SPN as positive and therefore probably malignant:

(I) A visually detectable metabolism;
(II) SUV_{max} >2.5 regardless of nodule diameter;
(III) SUV_{max} ≥1 if diameter ≤1 cm or SUV_{max} >2.5 if diameter >1 cm;
(IV) Ratio SUV_{max}/SPN diameter >1.

Final diagnosis

All patients underwent surgical resection of the SPN. A definitive pathologic diagnosis of the SPN, classifying the lesions as benign or malignant, was established.

Statistical analysis

Statistical analysis was performed using SPSS for windows version 19.0 (IBM, Armonk, New York, USA). All the comparisons were two-sided using a P value less than 0.05 to indicate statistical significance.

An independent *t*-test was used for comparing the age, diameter and SUV_{max} of the benign and malignant nodules, while that chi-square was used for smoking history, and gender. The diagnostic accuracy was obtained for each of the four different diagnostic approaches. A positive SPN classified by any of the four criteria was considered malignant in the metabolic assessment.

A receiver operating characteristic (ROC) curve analysis was performed to obtain the best cut-off of the SUV_{max} and SUV_{max}/diameter (diagnostic approaches III and IV), and the areas under curve (AUC) values of were obtained with a confidence interval (CI) of 95%.

Finally, we developed a model to estimate the probability of malignancy of patients with SPN by using stepwise logistic regression, with the final diagnosis as the dependent variable and the following independent variables: age, gender, smoking history (never *vs*. ever), nodule size, and SUV_{max}. Using backward selection, we achieved a final reduced model by eliminating variables that were not statistically significant at a level of 0.05. We used this final model to calculate the estimated probability of malignancy in each patient. We compared the predicted probability of malignancy with the final diagnosis and constructed a ROC curve. To describe the accuracy of the model for identifying malignancy in the patients, we reported the AUC with a CI of 95%.

Results

Fifty-five patients with SPN (45 men and 10 women, with a mean age of 62±11 years) were studied.

The pathologic analysis classified 40 (72.7%) of SPN as malignant and 15 (27.3%) as benign. From malignant SPN, the most prevalent histologies were: 65% adenocarcinoma, 17.5% epidermoid and 12.5% small cell carcinoma. Among the benign SPN, the most prevalent histologies were: 40% organizing pneumonia and 20% fibrosis. Patient demographics, smoking history and SPN characteristics attending the final pathologic diagnosis of the SPN are shown in *Tables 1* and *2*.

Mean ± standard deviation (SD) values of SPN diameter and SUV_{max} were 1.93±0.57 cm and 3.93±2.67, respectively.

There were statistically significant differences between the SUV_{max} values and patient age with the final histology of the SPN (malignant or benign). The mean ± SD of the SUV_{max} for benign nodules was 2.29±1.31 and 4.54±2.80 for malignant nodules (P=0.005). The mean patient age was 58±9 and 64±11 for benign and malignant SPN respectively, (P=0.045). No statistically significant differences were found for the rest of variables (*Table 3*).

Se, Sp and diagnostic accuracy for the different diagnostic criteria were (I): 97.5%, 13.1% and 74.5%; (II) 67.5%, 53.3% and 63.3%; (III) 70%, 53.3% and 64.5%; (IV) 85%, 33.3% and 70.9%, respectively.

ROC analysis showed an AUC for SUV_{max} and SUV_{max}/diameter of 0.75 and 0.79 (P <0.005), respectively.

The cutoff values with the best diagnostic performance were 1.95 (Se: 80%, Sp: 53.3%) and 1.04 (Se: 82.5%, Sp: 53.3%) for SUV_{max} and SUV_{max}/diameter, respectively. *Figure 1* shows the ROC curves.

Table 1 Patients' characteristics

Characteristic	Benign, n (%)	Malignant, n (%)
Number of patients	15 (27.3)	40 (72.7)
Age (mean ± SD)	58.0±9.1	64.2±11.1
Gender		
Male	14 (25.5)	31 (56.4)
Female	1 (1.8)	9 (16.4)
Smoking history		
Yes	15 (27.3)	35 (63.6)
No	0	5 (9.1)

SPN, solitary pulmonary nodule; SD, standard deviation.

Table 2 Pathologic results

Characteristic/Pathologic diagnosis	Number (%)
Malignant	40 (72.7)
Adenocarcinoma	26 (47.3)
Squamous cell carcinoma	7 (12.7)
Large cell carcinoma	1 (1.8)
Small cell carcinoma	5 (9.1)
Carcinosarcoma	1 (1.8)
Benign	15 (27.3)
Organizing pneumonia	5 (9.1)
Fibrosis	3 (5.5)
Hamartoma	2 (3.6)
Inflammatory pseudotumor	2 (3.6)
Granuloma	2 (3.6)
Lung abscess	1 (1.8)

Table 3 Univariate analysis of patients' data

Characteristic	Benign, n (%)	Malignant, n (%)	P
Patient age (years)	58±9.1*	64.2±11.1*	0.045
Gender			
Male	14 (25.5)	31 (56.4)	0.169
Female	1 (1.8)	9 (16.4)	
Smoking history			
No	0	5 (9.1)	0.189
Yes	15 (27.3)	35 (63.6)	
Nodule diameter (cm)	1.93±0.66*	1.92±0.53*	0.960
SUV_{max}	2.29±1.31*	4.54±2.80*	0.005

*, Values are mean ± standard deviation. SUV_{max}, maximum standard uptake value.

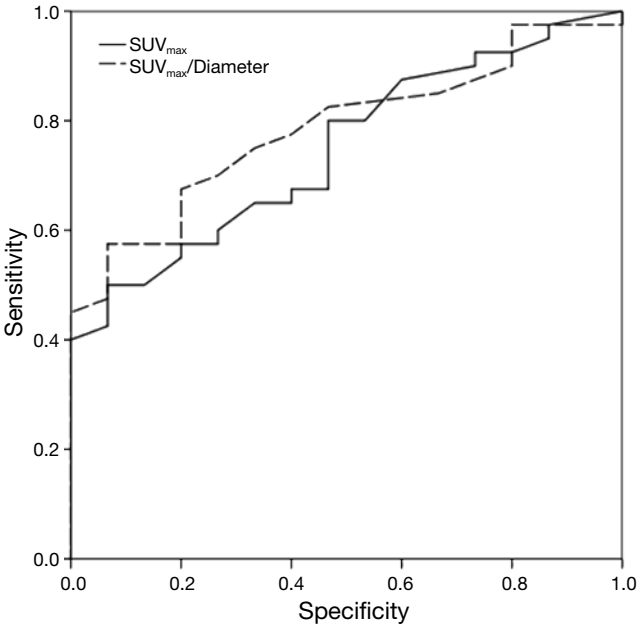

Figure 1 ROC curve of SUV_{max} and SUV_{max}/diameter methodologies. ROC, receiver operating characteristic; SUV_{max}, maximum standard uptake value.

By using univariate analysis, we identified that age and SUV_{max} were associated to malignity (*Table 3*). However, only SUV_{max} was an independent predictor in the multivariate analysis, with odd ratio of 1.6 and (95% CI, 1.01-2.417), see *Table 4*. Although age was not an independent variable, it was included in the predictive model, because its clinical importance, becoming to be an independent predictor in patients older than 60 years.

All other variables were not predictors of malignity, and therefore were not included in the final model. The prediction model is described by the following equations:

$$\text{Probability of malignancy of a SPN} = e^{x}/(1+e^{x}) \quad [1]$$

Where $x = -3.767 + (4.89 \times SUV_{max}) + (0.052 \times Age)$, e is the base of the natural logarithm, *Age* is the age in years and SUV_{max} is the maximum uptake value on the PET. The accuracy of the model was good with an AUC of the ROC curve of 0.793 (95% CI, 0.676-0.911, P<0.001), with Se and Sp of 87.5% and 46.7% respectively (*Figure 2*).

Discussion

The diagnosis of SPN remains a major challenge in medical practice. Detecting and diagnosing SPN is critical, as early identification of malignant nodules improves the chance for

Table 4 Multivariate logistic regression analysis

Factor	Regression coefficient	P value	Odds ratio value	95% CI	
				Lower	Upper
SUV_{max}	0.489	0.015	1.631	1.010	2.417
Age	0.052	0.100	1.053	0.988	1.123

CI, confidence interval; SUV_{max}, maximum standard uptake value.

successful treatment.

With regard to the FDG PET/CT imaging, some interpretation approaches have been assessed. Attending to visual assessment, a broad range of Se and Sp have been reported with values ranging from 69% to 100% and 63% to 85%, respectively (3,11,13,17). We found for the visual assessment (criterion I), a Se of 97.5%, it is in accordance with previously reported results, although the Sp (13.1%) was very limited, which is probably explained by the high prevalence of malignancy in our sample of patients. It is well know that higher the prevalence is, lower the risk of false positive results, and the prevalence will be higher as the inclusion of individuals in the screening program becomes more selective, focusing on higher clinical risk.

Abnormal ^{18}F-FDG uptake is not specific for malignancy; some benign lesions such as bacterial pneumonia, active sarcoidosis, infectious granulomas, acute pyogenic abscesses, cryptogenic fibrosing alveolitis, and so forth have been known to produce false-positive readings on PET (18). In our sample of patients, 27.3% of lesions were finally classified as benign, and from them the most prevalent were organizing pneumonia (40%), fibrosis (20%), and granulomas (13.3%). The median SUV_{max} for the benign lesions were 2.29±1.31, while that for malignant lesions were 4.54±2.80 (P<0.001).

In an attempt to improve the accuracy of the metabolic assessment some semiquantitative procedures have been developed. For instance, the uptake of the SPN (i.e., the glucose utilization) can be semiquantitatively assessed by the SUV_{max} and the uptake relative to the background activity in the uninvolved adjacent lung parenchyma and the mediastinum (19).

When we used a semiquantitative method, the Sp increased with a decreasing in sensibility and accuracy. The criterion (II), using a SUV cut-off of 2.5 regardless of the nodule size, had a sensibility, accuracy and Sp of 67.5%, 63.3% and 53.3% respectively. However, these parameters have been reported to be higher. A meta-analysis reported

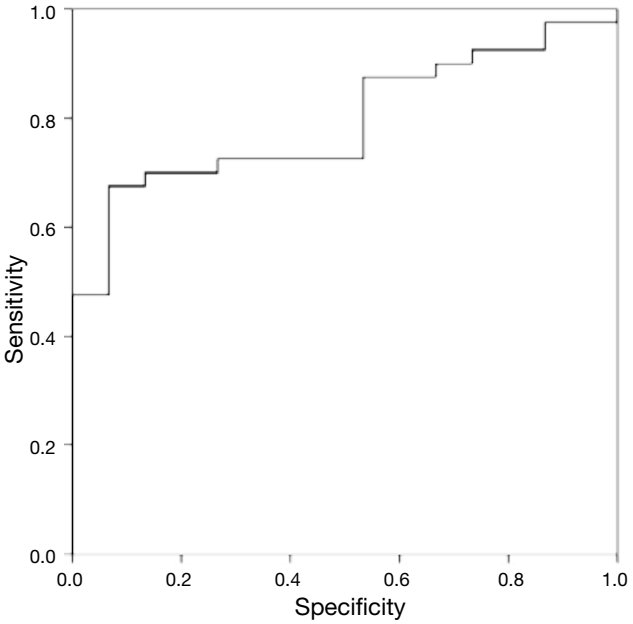

Figure 2 ROC curve of clinical data of the patients using our predictive model. ROC, receiver operating characteristic.

pooled Se of 95% (95% CI, 0.93-0.98) and Sp of 82% (95% CI, 0.77-0.88) to malignant nodules (10).

Partial volume effect and motion during the scan acquisition affects the uptake values measurement, especially for lesions smaller than about three times the spatial resolutions of the equipment, so partial volume and motion corrections factors for standardized PET uptake values may significantly change the differential diagnosis of small pulmonary nodules (20). In order to take into account volume partial effect, we used two different approximations to consider a SPN as malign, (criterion III): a variable threshold of SUV_{max} depending on the SPN diameter, and (criterion IV): the value obtained by dividing the SUV_{max} between the diameter of the nodule. This approach is justified, because SUV_{max} measure is affected by the nodule size, and although it is possible to use a recovery coefficient to have more accurate measurement (21), we use the nodule size, since it is proportional to the recovery coefficient.

The respiratory movement reduces the Se to detect pulmonary lesions; however, the synchronized acquisition of PET with respiratory movement (4D PET) can reduce this inconvenient. When the 4D PET is used to evaluate faint pulmonary lesions there is an increase of SUV_{max} respect to 3D (22,23). Even when this modality of acquisition was not used in our patient group, we expect to apply it to develop future works.

We aimed to assess the diagnostic accuracy of FDG-PET/CT, as well as to identify predictive factors of malignancy in SPN. With respect to the ROC analysis, the best cut-off for the SUV_{max} was 1.95 *vs.* 1.04 for the index SUV_{max}/diameter. Both values showed a Se of 80% and 82.5% respectively, with the same Sp (53.3%). There was an improvement of the diagnostic parameters, especially for the Sp. Our values of Se and Sp were similar to others published. For instance, Kim *et al.* (21) found that a SUV_{max} value of 2.5 had a Se and Sp of 89% and 51%, respectively, for all lesion sizes. Also Grgic *et al.* (13) obtained a Se and Sp of 96% and 55%, respectively.

Age has been reported to be one important risk factors for SPN malignancy (8,14). In our study, we found a statistically significant association between age and malignancy, as has been described. However, it was not an independent predictor of malignity.

The lesion diameter is also an important risk factor for malignancy. Numerous studies have confirmed this finding, always associating lesion growth with its malignant potential. Nodules of more than 20 mm in diameter have a greater than 50% chance of being diagnosed as malignant (20,24). This is not consistent with the findings of the present study, in which we did not find a significant association between lesion diameter and malignancy. We believe that the small size of the sample might have influenced this result.

Smoking has been found as independent predictor of malignancy (4,8,14). In our population the majority of patients had smoking history. Because of low percentage of non-smokers, our population was biased. It might have influenced the results, since we did not find relation between smoking history with the SPN malignancy. An interesting fact is that even, when the principal histological types related to smoking are squamous cell carcinoma and small cell carcinoma (25), we had low prevalence of these histologic types.

The retrospective nature of the study and the selection criteria could affect our results especially the latter. The fact that all the included patients with PET/CT were undergone surgery implied a high pre-test probability of malignancy that biases the PET/CT Sp. However, that warrantied the final histopathological confirmation of all lesions.

With regard to our results, a significant statistical difference between the SUV_{max} and patient age with final histology of SPN (benign and malignant) was found. This is in accordance with other studies (13,20). However, we found no statistically significant relation between malignancy and factors previously described as predictors of malignancy, such as smoking status, gender, and nodule diameter.

Predictive models of SPN malignancy is of major interest to clinicians. We derived a model to predict the probability of malignancy by a multivariate regression analysis, and identified the SUV_{max} as only independent predictors of malignancy of SPN. Our model had a Se and a Sp of 92.5% and 66.7%, respectively. Unlike other models (12,14,20), in which only clinical and morphological variables have been used, our model includes the SUV_{max} as a metabolic variable. The results obtained in this preliminary study allow us to conclude that the SUV_{max} is a good predictor of malignancy in a SPN and can be used in the diagnostic setting whenever available.

On the other hand, it will be necessary to develop new predictor models of malignancy based on clinical, morphological and metabolic variables, and test their validity.

The use of invasive diagnostic methods, such as fine-needle puncture, has risks to the patients, such as pneumothorax, bleeding and dissemination of the tumor along the trajectory of the needle (26). On the other hand, surgical lung biopsy has a mortality rate of around 0.6% (27). An accurate, robust and efficient predictive models for SPN malignity, it could provide clinicians with reliable information to avoid the need for an invasive diagnostic methods, allowing to limit the management of a SPN with a safe clinical monitoring.

Our predictive model of the SPN malignancy, unlike to other models, used the metabolic variable SUV_{max}, showing that it is an independent variable to predict malignancy. The diagnostic performance of this model was higher than visual and semiquantitative methodologies.

Conclusions

The assessment of SPN by semiquantitative methods did not improve the sensibility of visual analysis. The limited specificity was independent of the method used. However, the predictive model combining SUV_{max} and age was the best diagnostic approach, showing the SUV_{max} to be an independent variable to predict malignancy of a SPN.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

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Comparison between endobronchial ultrasound-guided transbronchial biopsy and CT-guided transthoracic lung biopsy for the diagnosis of peripheral lung cancer: a systematic review and meta-analysis

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Background: With the release of the National Lung Screening Trial results, the detection of peripheral pulmonary lesions (PPLs) is likely to increase. Computed tomography (CT)-guided percutaneous transthoracic needle biopsy (PTNB) and radial probe endobronchial ultrasound (r-EBUS)-guided transbronchial lung biopsy (TBLB) are recommended for tissue diagnosis of PPLs.

Methods: A systematic review of published literature evaluating the accuracy of r-EBUS-TBLB and CT-PTNB for the diagnosis of PPLs was performed to determine point sensitivity and specificity, and to construct a summary receiver-operating characteristic curve.

Results: This review included 31 publications dealing with EBUS-TBLB and 14 publications dealing with CT-PTNB for the diagnosis of PPLs. EBUS-TBLB had point sensitivity of 0.69 (95% CI: 0.67–0.71) for the diagnosis of peripheral lung cancer (PLC), which was lower than the sensitivity of CT-PTNB (0.94, 95% CI: 0.94–0.95). However, the complication rates observed with EBUS-TBLB were lower than those reported for CT-PTNB.

Conclusions: This meta-analysis showed that EBUS-TBLB is a safe and relatively accurate tool in the investigation of PLC. Although the yield remains lower than that of CT-PTNB, the procedural risks are lower.

Keywords: Computed tomography-guided percutaneous transthoracic needle biopsy (CT-PTNB); radial probe endobronchial ultrasound-guided transbronchial lung biopsy (r-EBUS-TBLB); peripheral pulmonary lesions; diagnosis; meta-analysis

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Introduction

With the established role of low-dose helical computed tomography (CT) screening for lung cancer (1,2) and the wide application of high-resolution CT (HRCT), pulmonary lesions are increasingly detected (3). Peripheral pulmonary lesions (PPLs) are a common problem in pulmonary practice. PPLs are defined as focal radiographic opacities that may be characterized as nodules (<3 cm) or masses (>3 cm). Solitary pulmonary nodule (SPN) is defined as a single, well-circumscribed radiographic opacity ≤30 mm in diameter that is completely surrounded by aerated lung and is not associated with atelectasis, hilar enlargement, or pleural effusion (4). With HRCT, PPLs can be categorized in a more accurate and detailed way. A ground-glass opacity (GGO) is a specific morphological type of pulmonary nodule (5).

To establish a tissue diagnosis, multiple approaches including sputum cytology, bronchoscopic sampling, and CT-guided percutaneous transthoracic needle biopsy (PTNB), may be undertaken. Conventional bronchoscopy has been used for several decades to diagnose PPLs (i.e., lesions that are not endobronchially visible), but its diagnostic yield is lower than 20% (6,7). The addition of imaging and guidance technology, such as radial probe endobronchial ultrasound (r-EBUS) and electromagnetic navigational bronchoscopy, has been shown by some studies to improve the diagnostic performance of transbronchial lung biopsy (TBLB). Several groups have now published their experience with r-EBUS-TBLB of PPLs. While there are a number of published case series evaluating the sensitivity and specificity of this diagnostic modality, the population recruited in each study was small and, therefore, the precision of the derived estimates varied widely. The aims of our study were to perform a systematic review of r-EBUS-TBLB and to ascertain the pooled sensitivity and specificity of this modality compared with published results of CT-PTNB for the diagnosis of peripheral lung cancer (PLC).

Methods

Publication search

Electronic databases of Medline (using PubMed as the search engine), Embase, Cochrane, and China National Knowledge Infrastructure were searched to identify suitable studies. Articles were identified with the use of the related articles function in PubMed. The references of the articles identified were also searched manually. The search terms used in this meta-analysis were "endobronchial ultrasound", "lung biopsy", "peripheral lung cancer", "peripheral pulmonary lesions", "computed tomography", "CT", "sensitivity and specificity", and "accuracy". An upper date limit of Aug 01, 2016 was applied; no lower date limit was used.

Inclusion criteria

We sought to identify all studies that used R-EBUS-TBLB and/or CT-PTNB for the investigation of PPLs. For inclusion, the studies must have met the following criteria: (I) evaluated the sensitivity (true-positive rate) and the specificity (false-positive rate) of r-EBUS-TBLB and/or CT-PTNB for the diagnosis of PPLs; (II) included at least 20 patients with PPLs for R-EBUS-TBLB and 200 patients with PPLs for CT-PTNB, since studies with smaller population may be vulnerable to selection bias; (III) histopathology analysis and/or close clinical follow-up for at least one year was used as the reference standard; and (IV) the search was performed without any restrictions on language and focused on studies that had been conducted in humans. Conference abstracts and letters to journal editors were excluded because of the limited data presented. Two reviewers (P Zhan and QQ Zhu) independently evaluated the study eligibility for inclusion. Disagreements were resolved by consensus.

Data extraction and quality assessment

The studies included were assessed independently by two reviewers who were blinded to publication details; disagreements were resolved by consensus. Extracted data included the following items: participant characteristics, publication year, patient enrolment and study design, use of reference standards, methodological quality, sensitivity data, and complication rate.

We assessed the methodological quality of the studies using guidelines published by the standards for reporting diagnostic accuracy (QUADAS) tool (8), with a maximum score of 14. Appraisal of the quality of the diagnostic accuracy of the primary studies was based on empirical evidence, expert opinion, and formal consensus.

Statistical analysis

The standard methods recommended for meta-analyses of diagnostic test evaluations were used (9). Meta-analyses

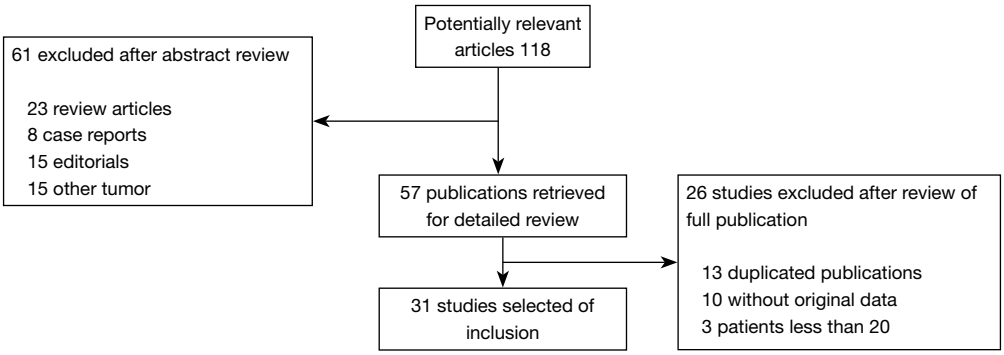

Figure 1 Identification, inclusion, and exclusion of studies on r-EBUS-TBLB. r-EBUS, radial probe endobronchial ultrasound; TBLB, transbronchial lung biopsy.

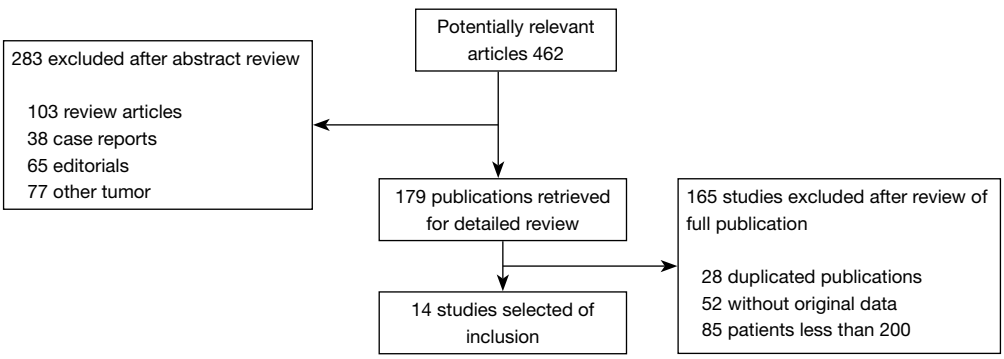

Figure 2 Identification, inclusion, and exclusion of studies on CT-PTNB. CT, computed tomography; PTNB, percutaneous transthoracic needle biopsy.

were performed using a statistical software program (Meta-DiSc Version 1.4; XI Cochrane Colloquium; Barcelona, Spain). We computed the following measures of test accuracy for each study: sensitivity; specificity; positive likelihood ratio (PLR); negative likelihood ratio (NLR); and diagnostic odds ratio (DOR).

The analysis was based on a summary receiver operating characteristic (SROC) curve (9,10). The sensitivity and specificity for the single test threshold identified for each study were used to plot an SROC curve (11). A random effects model was used to calculate the average sensitivity, specificity, and other measures across studies (12,13). The term heterogeneity, when used in relation to meta-analyses, referred to the degree of variability in results across studies. We used the χ^2 and Fisher exact tests to detect statistically significant heterogeneity, as appropriate. The relative DOR (RDOR) was calculated according to standard methods to analyze the change in diagnostic precision in a study per unit increase in the covariate (14,15).

Results

Study characteristics

After independent review, 31 publications (16-39) and (40-46) on r-EBUS-TBLB and 15 publications (47-61) on CT-PTNB for the diagnosis of PPLs were considered to be eligible for inclusion in the analysis. The study search process is shown in *Figures 1* and *2*. The QUADAS scores of these studies are outlined in *Table 1*. *Tables 2* and *3* present the principal characteristics of these studies. Among the 14 CT-PTNB publications, 12 were published in English and 2 were in Chinese. Among the 31 published studies on r-EBUS-TBLB, 29 were in English and 2 were in Chinese.

Diagnostic accuracy

Among 31 studies that evaluated the sensitivity of r-EBUS-TBLB for the diagnosis of PPLs, point sensitivity for pooled data was 0.69 (95% CI: 0.67–0.71) (*Figure 3*) and the area

Table 1 Main characteristics of selected studies on r-EBUS-TBLB

Author-year	No. of patients	Study design	Reference/comparison test	Q score
Herth-2002	50	Prospective randomizedcross-over study: EBUS versus fluoroscopy	Surgical resection	8
Yang-2004	122	Retrospective audit	Histology by alternate means or clinical surveillance	3
Shirakawa-2004	50	Prospective case series versus retrospective controls	Histology by alternate means	3
Kurimoto-2004	150	Prospective case series	Histology by alternate means	3
Paone-2005	87	Prospective, randomized, blinded study	Histology by alternate means	3
Asahina-2005	30	Unclear	Histology by alternate means	3
Herth-2006	54	Prospective case series	Surgical resection	4
Eberhardt-2007	39	Prospective RCT	Surgical resection	3
Yoshikawa-2007	121	Prospective case series	Histology by alternate means	3
Yamada-2007	155	Retrospective	NA	2
Asano-2008	31	Prospective case series	Surgical resection	3
Huang-2009	83	Retrospective audit	Histology by alternate means or surveillance	4
Eberhardt-2009	100	Prospective case series	Histology by alternate means	4
Oki-2009	86	Prospective study	Histology by alternate means or clinical surveillance	4
Chao-2009	88	Prospective, randomized trial.	NA	8
Disayabutr-2010	152	Prospective cross-sectional study	Histology by alternate means or clinical surveillance	6
Mizugaki-2010	107	Retrospective	Histology by alternate means or clinical surveillance	3
Steinfort-2011	51	Prospective randomized	Histology by alternate means or clinical surveillance	8
Fielding-2012	64	Prospective, randomized trial, EBUS-GS or CT-guided	Histology by alternate means or clinical surveillance	8
Hsia-2012	40	Retrospective	NA	2
Lin-2012	39	Retrospective	Surgical resection	3
Ishida-2012	65	Retrospective	NA	2
Oki-2012	203	Prospective EBUS-TBB under 3.4-mm or 4.0-mm thin bronchoscope with GS	Histology by alternate means or clinical surveillance	8
Fuso-2013	662	Retrospective	Histology by alternate means or clinical surveillance	3
Li-2014	75	Retrospective	Histology by alternate means	4
Chavez-2014	212	Retrospective	Histology by alternate means	4
Zhang-2015	117	Retrospective	Histology by alternate means	4
Durakovic-2015	147	Retrospective	Histology by alternate means or clinical surveillance	4
Tang-2016	105	Retrospective	Histology by alternate means or clinical surveillance	4
Fukusumi-2016	27	Retrospective	Histology by alternate means	4
Hayama-2016	27	Retrospective	Histology by alternate means or clinical surveillance	4

r-EBUS, radial probe endobronchial ultrasound; TBLB, transbronchial lung biopsy; Q, QUAD; NA, not applicable; CT, computed tomography.

Table 2 Characteristics of included studies on r-EBUS-TBLB

Study-year	No. of patients with LC	TP	FN	Complication	
				Severe bleeding	Pneumothorax with tube
Herth-2002	45	36	9	2	1
Yang-2004	122	80	42	NA	NA
Shirakawa-2004	24	17	7	NA	NA
Kurimoto-2004	101	82	19	0	0
Paone-2005	87	60	17	0	0
Asahina-2005	23	17	6	0	0
Herth-2006	39	28	11	0	1
Eberhardt-2007	32	23	9	0	2
Yoshikawa-2007	103	65	38	0	0
Yamada-2007	128	90	38	NA	NA
Asano-2008	27	23	4	NA	NA
Huang-2009	65	39	26	0	0
Eberhardt-2009	87	41	16	0	2
Oki-2009	44	35	9	0	0
Chao-2009	72	57	15	0	0
Disayabutr-2010	99	58	41	0	0
Mizugaki-2010	91	66	25	NA	NA
Steinfort-2011	32	25	7	0	0
Oki-2012	82	58	24	0	0
Fielding-2012	23	17	6	0	2
Hsia-2012	17	12	5	0	0
Lin-2012	39	30	9	NA	NA
Ishida-2012	50	38	12	0	1
Fuso-2013	359	255	104	NA	NA
Li-2014	32	27	5	0	0
Chavez-2014	212	143	69	0	0
Zhang-2015	88	66	22	0	0
Durakovic-2015	147	39	108	0	2
Tang-2016	14	12	2	0	0
Fukusumi-2016	18	12	6	NA	NA
Hayama-2016	27	20	7	0	0
Total complication (%)				0.087	0.48

r-EBUS, radial probe endobronchial ultrasound; TBLB, transbronchial lung biopsy; LC, lung cancer; TP, true-positive; FN, false-negative; NA, not applicable.

Table 3 Characteristics of included studies on CT-PTNB

Study-year	No. of patients with LC	Source	TP	FN	Complication (%)	
					Severe bleeding	Pneumothorax with tube
Yang-2015	217	China	215	2	11	3
Brandén-2014	463	Sweden	NA	NA	NA	27 patients (6%)
Lee-2014	766	Republic of Korea	733	33	1 patient	13 patients
Wang-2013	623	China	618	5	0	8 patients (1.3%)
Wang-2014	342	China	333	9	0	5 patients (1.5%)
Choi-2013	290	Republic of Korea	270	20	NA	NA
Loh-2013	399	Singapore	381	18	1 patient	12 patients (4.3%)
Yuan-2011	1014	China	962	52	1 patient	15 patients (1.5%)
Wei-2011	329	China	305	24	NA	NA
Laspas-2008	409	Greece	384	25	0	1 patient
D'Alessandro-2007	583	Italy	542	41	0	29 patients (18%)
Priola-2007	612	Italy	552	60	NA	NA
Tomiyama-2006	6881	Japan	NA	NA	22	14
Yeow-2003	631	China	587	44	NA	NA
Casamassima-1988	419	Italy	367	52	NA	NA
Total complication (%)					0.32	1.09

CT, computed tomography; PTNB, percutaneous transthoracic needle biopsy; LC, lung cancer; TP, true-positive; FN, false-negative; NA, not applicable.

under the SROC curve was 0.955 (SE =0.03) (*Figure 4*). Among 13 studies that evaluated the sensitivity of CT-PTNB for the diagnosis of PPLs, the point sensitivity for pooled data was 0.94 (95% CI: 0.94–0.95) (*Figure 5*) and the area under the SROC curve was 0.994 (SE =0.0023) (*Figure 6*).

Complication rates

The main limitation of CT-PTNB for the diagnosis of PPLs was the rate of complications, including pneumothorax and bleeding. The pooled rate across all included studies was 0.32% (36 out of 11,234) for severe bleeding and 1.09% (127 out of 11,697) for pneumothorax that needed chest tube drainage. On the other hand, the complication rates observed with r-EBUS-TBLB were low. The pooled rate across all included studies was 0.087% (2 out of 2,284) for severe bleeding and 0.48% (11 out of 2,284) for pneumothorax that needed chest tube drainage.

Discussion

The present meta-analysis showed that r-EBUS-TBLB had a point sensitivity of 0.69 (95% CI: 0.67–0.71) for the diagnosis of PLC, which was lower than the sensitivity of CT-PTNB (0.94, 95% CI: 0.94–0.95). Although the diagnostic yield was not superior to that of CT-PTNB, the major advantage of r-EBUS-TBLB over CT-PTNB was its safety profile. Our meta-analysis demonstrated overall rates of only 0.087% for severe bleeding and 0.48% for pneumothorax that needed chest tube drainage. In comparison, many studies describing CT-PTNB reported 0.32% rate of severe bleeding and 1.09% overall rate for pneumothorax requiring chest tube drainage.

Since Haaga and Alfidi reported the first case of CT-PTNB in 1976 (62), the procedure had been constantly developed and is currently widely employed as a routine diagnostic technique for PPLs, owing to its simplicity and minimal invasiveness. Recently, we performed a

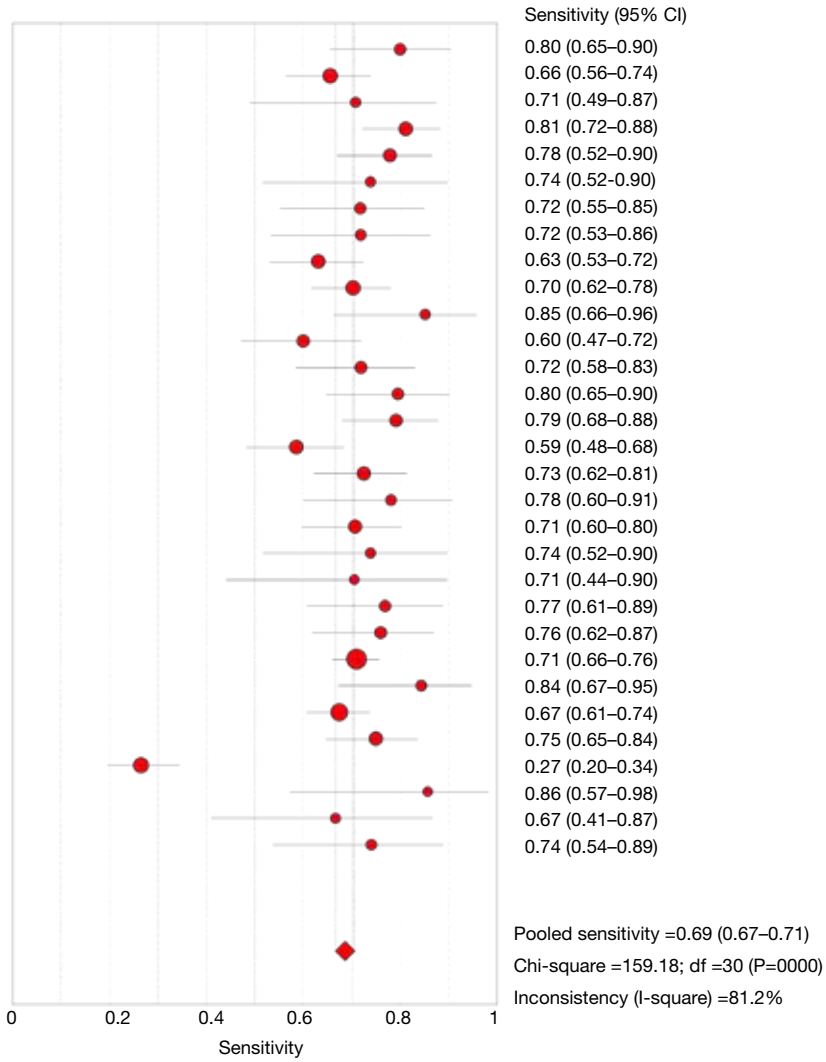

Figure 3 Forest plot: sensitivity analysis for of r-EBUS-TBLB for the diagnosis of PPLs. r-EBUS, radial probe endobronchial ultrasound; TBLB, transbronchial lung biopsy; PPL, peripheral pulmonary lesion.

retrospective study (47) to evaluate the diagnostic accuracy of CT-PTNB for SPN. Out of the 311 patients with SPN, 2 were false-positive cases, 12 were false-negative cases, and 8 were undiagnosed, resulting in a 92.9% diagnostic accuracy of CT-PTNB. However, PTNB has been known to have major complications of pneumothorax and pulmonary hemorrhage, with reported incidence rates of 10%~40% and 26%~33%, respectively (63). In our previous study (47), there were 55 cases of pneumothorax (17.7%), 2 cases needed thoracentesis and 1 case needed chest tube drainage. In addition, the diagnostic yield was influenced by size of the lesion, size of the needle, number of passes, and use of rapid on-site evaluation (64,65).

On the other hand, conventional bronchoscopy for PPLs can be performed using several instruments and sampling methods, including transbronchial biopsy forceps, transbronchial brush, transbronchial needle aspiration, and bronchoalveolar lavage. However, the sensitivity of traditional bronchoscopic biopsy was only 14%~34% for nodules <2 cm (66). The sensitivity increased to 63% when nodules were >2 cm in size, but decreased as the distance from the hilum increased. Recently, image guidance has been used during bronchoscopy. One of which is r-EBUS that uses a 20-MHz ultrasound probe that can be passed through the working channel of a bronchoscope into the lung periphery. The r-EBUS probe can be passed within

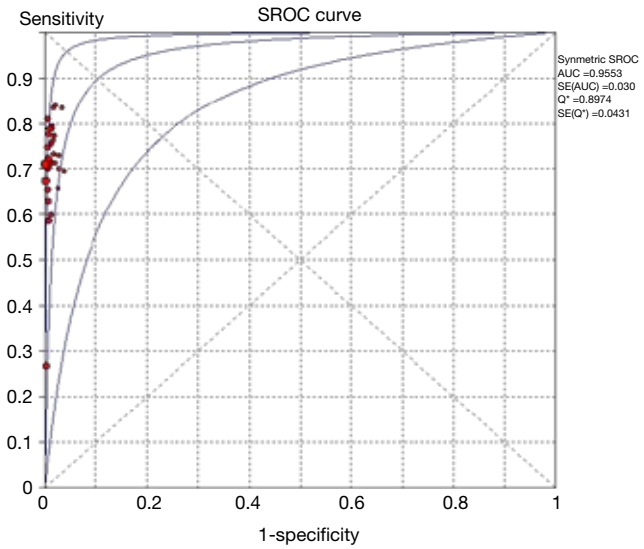

Figure 4 Summary receiver operating characteristics plot: r-EBUS-TBLB for the diagnosis of PPLs. r-EBUS, radial probe endobronchial ultrasound; TBLB, transbronchial lung biopsy; PPL, peripheral pulmonary lesion.

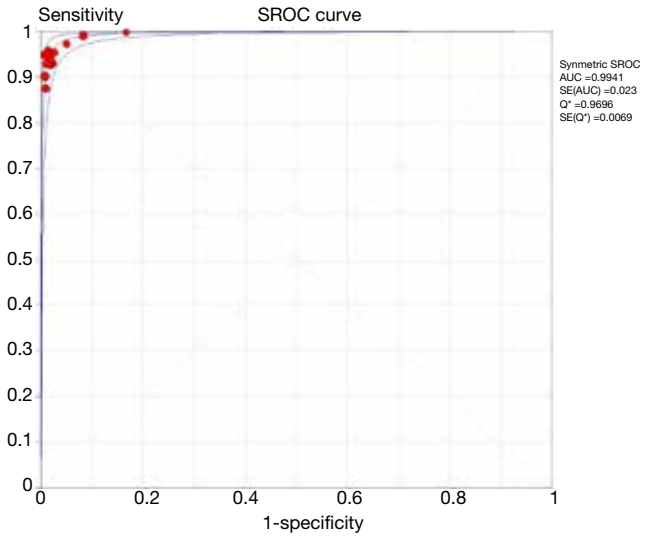

Figure 6 Summary receiver operating characteristics plot: CT-PTNB for the diagnosis of PPLs. CT, computed tomography; PTNB, percutaneous transthoracic needle biopsy; PPL, peripheral pulmonary lesion.

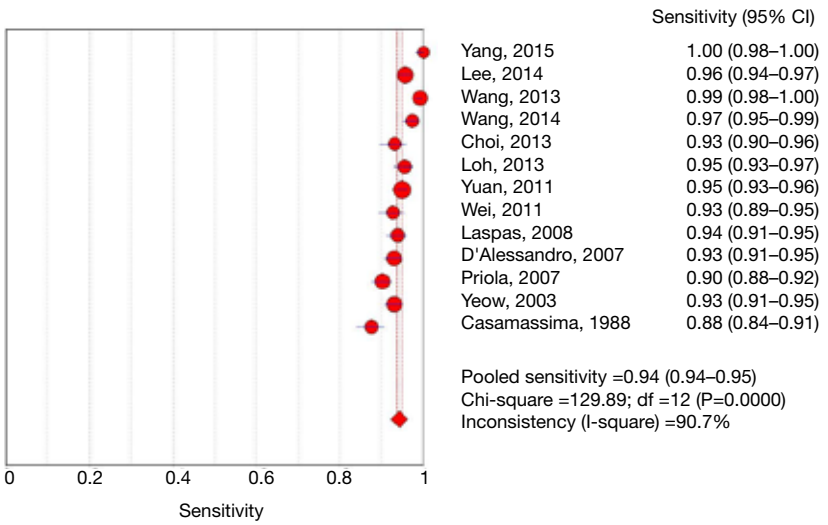

Figure 5 Forest plot: sensitivity analysis for of CT-PTNB for the diagnosis of PPLs. CT, computed tomography; PTNB, percutaneous transthoracic needle biopsy; PPL, peripheral pulmonary lesion.

a disposable guide sheath or by itself. Two previous meta-analyses have evaluated the performance of r-EBUS for the investigation of PPLs. The one by Steinfort *et al.* (67) on 16 studies of 1,420 patients that underwent r-EBUS for diagnosis of PPLs showed a pooled sensitivity of 73% (95% CI: 70%~76%). Another meta-analysis (68) reported pooled diagnostic yields of 73.2% (95% CI: 64.4%~81.9%) for r-EBUS with a guide sheath and 71.1% (95% CI: 66.5%~75.7%) for r-EBUS without a guide sheath.

It has been reported that several guided-bronchoscopy technologies could improve the yield of transbronchial biopsy for PPLs diagnosis, such as electromagnetic navigation bronchoscopy (ENB), virtual bronchoscopy (VB), r-EBUS, ultrathin bronchoscope, and guide sheath.

Wang Memoli *et al*. study (68) performed the meta-analysis to determine the overall diagnostic yield of guided bronchoscopy using one or a combination of these technologies. They found that the pooled diagnostic yield was 70%, which is higher than the yield for traditional transbronchial biopsy. The yield increased as the lesion size increased. Only a few studies have focused on impact of the "bronchus sign", defined as a bronchus leading directly into the lesion on transverse CT imaging, although we have recognised the importance of the "bronchus sign" for the diagnosis of PPLs within our own practice.

The major limitation of our findings was the quality of studies included in the meta-analysis. The consistency of the patient populations in the individual studies was unclear because the selection criteria were not clear in the majority of studies. Therefore, it is difficult to know whether the spectrum of study subjects was representative of patients who would undergo r-EBUS-TBLB in clinical practice. In addition, some factors influencing the performance of r-EBUS-TBLB were not described in most papers included in our meta-analysis. These factors include bronchoscopist experience, number of biopsies taken, proximity of the PPL to central airways, and radiologic appearance of PPLs.

In summary, our meta-analysis confirmed that the overall diagnostic performance of r-EBUS-TBLB for PPLs was relatively accurate, although lower than that of CT-PTNB. However, our results indicate a favorable safety profile of EBUS-TBLB, supporting EBUS-TBLB as a viable investigation in patients with PPLs. This data once more suggests that radial EBUS may be the initial test of choice for the diagnosis of PPLs in those patients deemed at higher risk of a pneumothorax from CT-PTNB such as in the context of severe emphysema. The diagnostic sensitivity of r-EBUS-TBLB may be influenced by the prevalence of malignancy in the patient cohort being examined. Further randomized-controlled trials are required to evaluate the generalizability of our results to more clearly defined patient populations.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Correlation in histological subtypes with high resolution computed tomography signatures of early stage lung adenocarcinoma

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Background: Uncertainty remains on the association between image characteristics of the nodules in computed tomography (CT) scans and lung adenocarcinoma histopathologic subtypes. We aimed to estimate the correlation between preoperative high resolution computed tomography (HRCT) scan and postoperative histopathology of stage IA lung adenocarcinoma in East Asian Chinese population.

Methods: We retrospectively reviewed the clinical records and HRCT images of 190 patients (106 female and 84 male) with resected, preoperatively untreated stage IA adenocarcinomas. The relationship between image characteristics of nodules at preoperative HRCT and their histological subtypes after resection were analyzed. The one-way ANOVA, chi-square test and logistic regression were used for analysis.

Results: In 190 patients with stage IA lung adenocarcinoma, median tumor diameter was significantly lower in lepidic predominant invasive adenocarcinoma (LPA) (15.96±6.95 mm). Univariate analysis revealed that ground-glass opacity (GGO) proportion (P<0.001), margin (P<0.001), border definition (P=0.015), pleural retraction (P<0.001) and enhancement (P<0.001) had statistically significant differences in four histological subtypes. The multivariate analysis referenced for lepidic group which indicated that GGO proportion and pleural retraction were independent associated with acinar group (RR=4.221, 95% CI: 1.770–10.066, P=0.001; RR=0.380, 95% CI: 0.158–0.916, P=0.031, respectively). Male and whose nodule margin with spiculation or lobulation were prone to papillary predominant invasive adenocarcinoma (PPA) (RR=0.288, 95% CI: 0.090–0.920, P=0.036; RR=0.250, 95% CI: 0.070–0.887, P=0.032, respectively). GGO proportion and nodule margin were independent related factors in solid predominant invasive adenocarcinoma (SPA) (RR=13.338, 95% CI: 2.974–59.811, P=0.001; RR=0.097, 95% CI: 0.016–0.606, P=0.013, respectively).

Conclusions: Nodules with spiculation or lobulation and less GGO proportion are determinants of histological subtypes with poor prognosis in stage IA lung adenocarcinoma patients according to the 2011 histologic IASLC/ATS/ERS classification.

Keywords: High resolution computed tomography (HRCT); lung adenocarcinoma; histopathology; ground-glass opacity (GGO)

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Introduction

Lung cancer is the most frequently diagnosed cancer and remains a leading cause of cancer death worldwide (1). While lung adenocarcinoma is the most common histological subtype (2). In 2011 Feb, International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) jointly published a newly lung adenocarcinoma classification. The classification addresses both resection specimens and small biopsies/cytology. New concepts such as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) were added. And invasive adenocarcinomas (IA) were classified with lepidic, acinar, papillary, micropapillary, and solid patterns Travis *et al*. (3). According to this new classification, patients who have AIS, MIA, and lepidic predominant adenocarcinomas have shown excellent survival rates after complete resection.

The National Lung Screening Trial (NLST) found a relative reduction in mortality from lung cancer with low-dose computed tomography (CT) screening of 20.0% compared with chest radiography (4). While on CT scans, these indolent and less aggressive tumors of AIS, MIA, and lepidic predominant adenocarcinomas frequently present as pure ground-glass opacity (pGGO) or mixed ground-glass opacity (mGGO) (5). Several other studies confirmed a well correlation between CT findings and histologic prognostic factors in lung adenocarcinomas (5-7). However, when pGGOs are greater than 15 mm in diameter or have high pixel attenuation (>–472 HU), the nodules are more likely to be IA (8). Recently, a similar observation has been documented for early stage tumors about GGO component. They found that in patients with tumors smaller than 3 cm, disease free survival (DFS) was significantly associated with solid tumor size, but not with whole tumor size (9).

GGO proportion is very important for prognosis in lung adenocarcinoma. Previous studies have explored CT features correlating with pathological invasiveness. They reported that tumors with higher solid volume proportion and larger diameter indicated IA rather than non-invasive lesions (AIS and MIA) (10-12). Nevertheless, uncertainty remains on the correlation between image characteristics of the nodules in CT scans and adenocarcinoma histopathologic subtypes.

We performed this retrospective analysis to estimate the correlation between preoperative high resolution computed tomography (HRCT) scan and postoperative histopathology of stage IA lung adenocarcinoma in East Asian Chinese population. In addition, we'd like to find some independent risk factors in HRCT signatures which can help distinguish histological subtypes in early stage lung adenocarcinoma to predict their prognosis.

Methods

Patients

We retrospectively reviewed the clinical records and CT images of 190 patients (106 female and 84 male; age range, 29–81 years; average age, 59 years) with resected, preoperatively untreated pT1N0M0 stage IA adenocarcinomas. These patients underwent lung cancer surgery in Jinling hospital (Jiangsu, China) between July 2008 and March 2015. All cases met the 2011 IASLC/ATS/ERS classification (3) of lung adenocarcinomas and were considered as stage IA according to the 7th Edition Union for International Cancer Control/American Joint Committee on Cancer TNM classification (13). Patients concurrent with other tumors were excluded (*Figure 1*).

Histological evaluation

Histological classification was according to the IASLC/ATS/ERS classification of lung adenocarcinomas (3). Tumors were classified as atypical adenomatous hyperplasia (AAH), AIS, MIA and IA. IA was further divided into lepidic predominant, acinar predominant, papillary predominant, micropapillary predominant, solid predominant with mucin, invasive mucinous adenocarcinoma and colloid predominant.

HRCT evaluation

Two radiologists with 3 years of experience retrospectively interpreted the HRCT images independently. If they have different opinions, a third radiologist will confirm it. Margin characteristics of nodules and the internal characteristics within the nodules were all analyzed. These characteristics included diameter, proportion of GGO, margin, border definition, bubble lucency, shape, air bronchogram, vessel convergence sign, pleural retraction, pleural thickening, lymphadenopathy, enhancement and so on. GGO was defined as hazy and amorphous increased lung attenuation without obscuration of the underlying vascular markings and bronchial walls. In regard to evaluated the GGO proportion of the tumor (GGO/tumor ratio; G/T ratio),

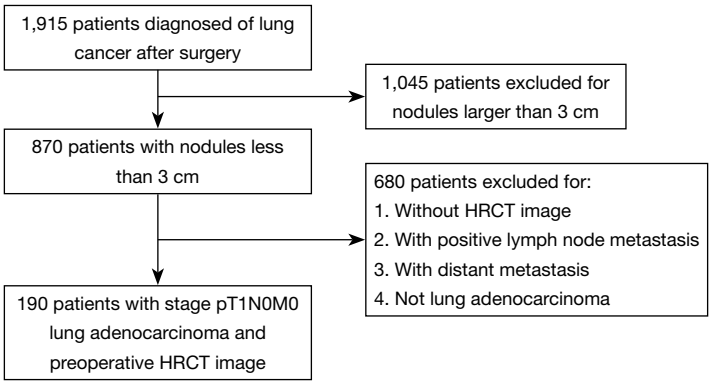

Figure 1 Selection process for stage pT1N0M0 lung adenocarcinoma with high resolution computed tomography (HRCT) image.

the G/T ratio was calculated as (1-DSOL)/ DGGO, where DGGO was the largest area of the tumor, and DSOL was the largest solid area of the tumor (14).

Statistics

Statistical analysis was performed using the one-way ANOVA for continuous variables and chi-square test for categorical variables. To analyze the relationship between HRCT and histological subtypes, we used logistic regression model for multivariate analysis. Values of P<0.05 were considered significant. Statistical analysis was conducted using Statistical Product and Service Solutions (SPSS) version 20.0.

Results

Clinical characteristics

Clinical features including sex, age, smoking history, tumor location, surgical procedures, and histological subtype were summarized in *Table 1*. Most patients were female (56%) and never smoking (71%). Median age was 59 years (range, 29–81 years). A large majority of tumors (65%) were located in right lung. Seventy four tumors (39%) were located in right upper lobe (RUL) and 46 tumors (24%) were located in left upper lobe (LUL). One hundred and sixty one patients (85%) underwent lobectomy, 22 patients (12%) underwent wedge resection, and 7 patients (4%) underwent segmentectomy (*Table 1*). No patient received preoperative adjuvant chemotherapy and/or radiation therapy. Among the patients, 55 received *EGFR* mutation detection, 32 (58%) of them were *EGFR* mutation positive (*Table 2*).

Histological characteristics

According to the IASLC/ATS/ERS classification, there were 2 AAH cases (1%), 3 AIS cases (2%), 10 MIA cases (5%) and 175 IA cases (92%) which were mostly acinar predominant adenocarcinoma (44%) (*Table 1*).

Since solid adenocarcinomas have a poor prognosis, papillary and acinar adenocarcinomas have an intermediate prognosis, and lepidic adenocarcinomas have a favorable prognosis (15). In order to better carry out statistics, we classified lung adenocarcinoma in four groups. Lepidic group contains AAH, AIS, MIA and lepidic predominant IA. Acinar group is acinar predominant IA. Papillary group is papillary predominant IA. And solid group is solid predominant invasive adenocarcinoma (SPA).

Univariate analysis

We conducted one-way ANOVA analysis to find the differences among four groups. Median tumor diameter was 19.58±7.33 mm, and it was significantly lower in level 1 group (15.96±6.95 mm), whereas acinar predominant adenocarcinoma and papillary-predominant (21.28±7.18 mm; 19.90±6.85 mm, respectively) were of intermediate size, and level 4 (21.70±6.49 mm) were larger (P<0.001). GGO proportion (P<0.001), margin (P<0.001), border definition (P=0.015), pleural retraction (P<0.001) and enhancement (P<0.001) had statistically significant differences in four histological levels (*Table 2*). There were no significant differences in bubble lucency, shape, air bronchogram, vessel convergence sign, pleural thickening, lymphadenopathy and *EGFR* mutation by chi-square test (*Table 2*).

Table 1 Clinical characteristics of patients with pT1N0M0 lung adenocarcinoma

Characteristics	Overall (n=190, %)
Sex	
Female	106 [56]
Male	84 [44]
Age (years)	
<50	33 [17]
50–59	63 [33]
60–69	65 [34]
≥70	29 [15]
Median [range]	59 [29–81]
Smoking history	
No	135 [71]
Yes	55 [29]
Tumor location	
RUL	74 [39]
RML	10 [5]
RLL	39 [21]
LUL	46 [24]
LLL	21 [11]
Surgical procedures	
Wedge resection	22 [12]
Segmentectomy	7 [4]
Lobectomy	161 [85]
Histological subtype	
AAH	2 [1]
AIS	3 [2]
MIA	10 [5]
LPA	40 [21]
APA	83 [44]
PPA	29 [15]
SPA	23 [12]

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; LPA, lepidic predominant invasive adenocarcinoma; APA, acinar predominant invasive adenocarcinoma; PPA, papillary predominant invasive adenocarcinoma; SPA, solid predominant invasive adenocarcinoma.

Multivariate analysis

To find the association between HRCT characteristics and histological subtypes, we conducted the multivariate analysis referenced for lepidic group which indicated that GGO proportion and pleural retraction were independent associated with acinar group (RR=4.221, 95% CI: 1.770–10.066, P=0.001; RR=0.380, 95% CI: 0.158–0.916, P=0.031, respectively, *Table 3*). Tumors which HRCT characterized without GGO component and with positive pleural retraction were more likely to be acinar predominant IA than lepidic predominant IA. While male and whose nodule margin with spiculation or lobulation were prone to papillary predominant IA (RR=0.288, 95% CI: 0.090–0.920, P=0.036; RR=0.250, 95% CI: 0.070–0.887, P=0.032, respectively, *Table 3*). GGO proportion and nodule margin were independent prediction factors in solid group (RR=13.338, 95% CI: 2.974–59.811, P=0.001; RR=0.097, 95% CI: 0.016–0.606, P=0.013, respectively, *Table 3*). Nodules without GGO component or nodule margin with spiculation or lobulation were risk factors for poor prognosis histological subtypes.

Discussion

In this study, we retrospectively reviewed 190 patients with preoperatively untreated pT1N0M0 stage IA adenocarcinomas in East Asian Chinese population, and investigated a number of prediction factors in clinical and HRCT scan between different histological subtypes.

In univariate analysis, we found that smaller tumor size and larger GGO proportion were significantly associated with indolent and less aggressive tumors. Similarly, there were several studies also found that the size and mass of the nodule are determinants of invasive adenocarcinoma (8,16-18). While, recently an observation found that in patients with tumors smaller than 3 cm, DFS was significantly associated with solid tumor size, but not with whole tumor size in early stage tumors (9). They suggested that nomogram-based T descriptors provide better prediction of survival than conventional T descriptors (9). Our results thus are in concordance with previous findings and support the hypothesis that larger tumor size and smaller GGO proportion are risk factors for poor prognosis histological subtypes in early stage lung adenocarcinomas. In addition, we have shown that tumors with spiculation or lobulation, poorly defined border and positive pleural retraction were more likely to be poor prognosis histological

Table 2 Univariate analysis of HRCT characteristics and lung adenocarcinoma histologic subtypes

HRCT characteristics	Number	Histologic subtype[#]				χ^2/F	P value
		Lepidic	Acinar	Papillary	Solid		
All patients	190	55 (29%)	83 (44%)	29 (15%)	23 (12%)		
Diameter (mm)*	19.58±7.33	15.96±6.95	21.28±7.18	19.90±6.85	21.70±6.49	7.297	<0.001
Proportion of GGO (%)						43.721	<0.001
0	115	16	62	17	20		
1–50	27	9	11	5	2		
51–100	48	30	10	7	1		
Margin						22.805	<0.001
Smooth	49	27	15	5	2		
Spiculation or lobulation	141	28	68	24	21		
Border definition						10.487	0.015
Poorly defined	69	28	30	7	4		
Well defined	121	27	53	22	19		
Bubble lucency						1.643	0.650
–	128	40	52	20	16		
+	62	15	31	9	7		
Shape						7.266	0.064
Round	131	41	49	22	19		
Irregular	59	14	34	7	4		
Air bronchogram						3.081	0.379
–	114	38	45	17	14		
+	76	17	38	12	9		
Vessel convergence sign						2.456	0.483
–	160	47	70	22	21		
+	30	8	13	7	2		
Pleural retraction						20.907	<0.001
–	79	34	20	13	12		
+	111	21	63	16	11		
Pleural thickening						5.259	0.154
–	166	51	70	23	22		
+	24	4	13	6	1		
Lymphadenopathy						1.112	0.774
–	154	44	68	22	20		
+	36	11	15	7	3		
Enhancement						19.044	<0.001
–	36	15	16	5	0		
+	94	11	50	15	18		
EGFR mutation						6.125	0.106
–	23	6	8	4	5		
+	32	8	19	4	1		

[#], lepidic group contains AAH, AIS, MIA and LPA. Acinar group is APA. Papillary group is PPA. Solid group is SPA; *, diameter analysis used the one-way ANOVA analysis, others used chi-square test; HRCT, high resolution computed tomography; GGO, ground-glass opacity; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; APA, acinar predominant invasive adenocarcinoma; LPA, lepidic predominant invasive adenocarcinoma; PPA, papillary predominant invasive adenocarcinoma; SPA, solid predominant invasive adenocarcinoma.

Table 3 Multivariate analyses of clinical/HRCT characteristics and lung adenocarcinoma histologic subtype

Histologic subtype[#, *]	P value	RR	95% CI
Acinar			
Sex			
Female	0.089	2.632	0.863–8.029
Male	Reference	–	–
Smoking			
No	0.150	0.399	0.114–1.395
Yes	Reference	–	–
GGO proportion (%)			
0	0.001	4.221	1.770–10.066
1–100	Reference	–	–
Margin			
Smooth	0.370	0.650	0.254–1.666
Spiculation or lobulation	Reference	–	–
Pleural retraction			
No	0.031	0.380	0.158–0.916
Yes	Reference	–	–
Pleural thickening			
No	0.715	0.787	0.218–2.844
Yes	Reference	–	–
Papillary			
Sex			
Female	0.036	0.288	0.090–0.920
Male	Reference	–	–
Smoking			
No	0.380	1.832	0.474–7.076
Yes	Reference	–	–
GGO proportion (%)			
0	0.223	2.008	0.654–6.165
1–100	Reference	–	–
Margin			
Smooth	0.032	0.250	0.070–0.887
Spiculation or lobulation	Reference	–	–
Pleural retraction			
No	0.799	1.149	0.394–3.349
Yes	Reference	–	–
Pleural thickening			
No	0.401	0.522	0.115–2.378
Yes	Reference	–	–
Solid			
Sex			
Female	0.327	0.428	0.079–2.331
Male	Reference	–	–
Smoking			
No	0.207	0.341	0.064–1.816
Yes	Reference	–	–
GGO proportion (%)			
0	0.001	13.338	2.974–59.811
1–100	Reference	–	–
Margin			
Smooth	0.013	0.097	0.016–0.606
Spiculation or lobulation	Reference	–	–
Pleural retraction			
No	0.069	3.298	0.911–11.934
Yes	Reference	–	–
Pleural thickening			
No	0.081	8.982	0.761–106.075
Yes	Reference	–	–

[#], lepidic group contains AAH, AIS, MIA and LPA. Acinar group is APA. Papillary group is PPA. Solid group is SPA; *, the reference category is: lepidic group. HRCT, high resolution computed tomography; RR, relative risk; CI, confidence interval; GGO, ground-glass opacity; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; LPA, lepidic predominant invasive adenocarcinoma; APA, acinar predominant invasive adenocarcinoma; PPA, papillary predominant invasive adenocarcinoma; SPA, solid predominant invasive adenocarcinoma.

subtypes. Not all patients took enhanced CT examination, but tumors with enhancement were significantly relevant with acinar predominant IA.

However, we did not find significant difference in bubble lucency, shape, air bronchogram, vessel convergence sign, pleural thickening, lymphadenopathy in *EGFR* mutation (*Table 2*). While, different observations were found last year (19,20). One of the studies enrolled 35 patients with 72 lesions. Among them, 33 (45.8%) tumor lesions were found harboring *EGFR* mutations, and their founding indicated that there was a high discrepancy of driver mutations in NSCLC patients with ground-glass nodules (GGNs) (19). Another research showed that *EGFR* mutation especially L858R was detected more frequently in invasive solid pattern and significantly less in pure GGO pattern in stage I lung adenocarcinoma (21). In our study, 55 patient conducted EGFR detection, only 9 of them were pGGOs. Although there was no significant difference, a majority of patients with positive *EGFR* mutation were acinar predominant IA (59%) (*Table 2*).

In multivariate analysis, we used lepidic group (histological subtypes with favorable prognosis) as reference for logistic regression model. Tumors which HRCT characterized without GGO component and with positive pleural retraction were more likely to be acinar predominant IA than lepidic predominant IA. Male and whose nodule margins with spiculation or lobulation were prone to papillary predominant IA. Solid nodules without GGO component or nodule margin with spiculation or lobulation were prediction factors for poor prognosis histological subtypes.

Our results suggest that GGO proportion, margin signature and pleural retraction should be focused initial evaluation of histological subtypes in early stage lung adenocarcinomas. Several studies also showed that proportion of GGO remains important for predicting less invasive lung cancer (22-24). In their opinion, small peripheral adenocarcinoma or BAC may present with a high ratio of GGO components on CT scans. Investigators have reported that the solid components in advanced-stage lesions are significantly larger than those in lesions at earlier stage (5,25). Solid component increases the level of suspicion for invasive adenocarcinoma. Our study firstly evaluated the correlation between HRCT image and four histological subtypes.

However, we did not find significant difference in smoking history (*Table 3*). Recent studies have showing that smoking was a significant predictive for unfavorable prognosis in lung adenocarcinoma (26). And it was robustly associated with GGO growth (27). In our study, most patients were female (56%) (*Table 1*). We could not exclude passive smoking and exposure to dust (28) from those without smoking history. Besides, air pollution may be another reason.

This study had some limitations. First, this was a retrospective study and the number of patients was relatively small for our strict inclusion criteria. And some cases were excluded for not available HRCT image in other hospitals. We hope to further validate these results in a prospective study with a large number of cases. Second, since our study reviewed patients between July 2008 and March 2015, we could not get complete prognostic information now. We look forward to confirm these results and find more useful risk factors in early stage lung adenocarcinoma prognosis by follow-up research.

In conclusion, we demonstrated that nodules with spiculation or lobulation and less GGO proportion are determinants of poor prognosis histological subtypes in stage IA lung adenocarcinoma patients according to the 2011 histologic IASLC/ATS/ERS classification. HRCT signatures such as tumor diameter, GGO proportion, margin, border definition and pleural retraction may help infer histological subtypes of lung adenocarcinoma in early stage.

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Footnote

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Lung cancer diagnosis and staging in the minimally invasive age with increasing demands for tissue analysis

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Abstract: The diagnosis and staging of patients with lung cancer in recent decades has increasingly relied on minimally invasive tissue sampling techniques, such as endobronchial ultrasound (EBUS) or endoscopic ultrasound (EUS) needle aspiration, transbronchial biopsy, and transthoracic image guided core needle biopsy. These modalities have been shown to have low complication rates, and provide adequate cellular material for pathologic diagnosis and necessary ancillary molecular testing. As an important component to a multidisciplinary team approach in the care of patients with lung cancer, these minimally invasive modalities have proven invaluable for the rapid and safe acquisition of tissue used for the diagnosis, staging, and molecular testing of tumors to identify the best evidence-based treatment plan. The continuous evolution of the field of lung cancer staging and treatment has translated into improvements in survival and quality of life for patients. Although differences in clinical practice between academic and community hospital settings still exist, improvements in physician education and training as well as adoption of technological advancements should help narrow this gap going forward.

Keywords: Lung cancer; staging; molecular testing; minimally invasive; endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA); interventional pulmonology

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Introduction

Lung cancer is the leading cause of cancer deaths worldwide. The most frequently encountered primary lung cancers include epithelial-derived non-small-cell lung cancer (NSCLC), with adenocarcinoma and squamous cell carcinoma as the main histologic subtypes; and neuroendocrine carcinomas, with small cell lung cancer (SCLC) as the major high-grade neuroendocrine carcinoma. Most NSCLCs are diagnosed at advanced stages, and historically (up to the early 2000s), palliative therapeutic decisions were based solely on the differentiation between NSCLC and SCLC. Hence, the main diagnostic modalities and focus on tissue acquisition were geared towards obtaining small samples for simple histopathological characterization that would be added to non-invasive imaging studies to complete tumor, node, metastasis (TNM) staging. The paradigm of NSCLC histology not otherwise specified (NOS) with advanced TNM staging drove the development of anti-cancer therapies for NSCLCs in the 1980s, 1990s, and early 2000s; with the evidence-based introduction of platinum-doublets as the main palliative modality for stage IV NSCLC (1).

A need to better define NSCLC subtypes occurred in the early 2000s with the introduction of novel cytotoxic chemotherapies (pemetrexed) and biological agents

(bevacizumab) that had enhanced efficacy or worsened toxicity, respectively, based on histology (2,3). To this end, a diagnosis of NSCLC NOS was no longer sufficient, and the more widespread use of both histochemical and immunohistochemical ancillary studies helped to more consistently distinguish adenocarcinoma from squamous cell carcinoma in small biopsy/cytology specimens. The 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) lung adenocarcinoma classification was developed by an international core panel of expert medical oncologists, pulmonologists, pathologists, and thoracic surgeons, to address minimum requirements in immunohistochemical testing markers to differentiate between adenocarcinoma and squamous cell in small samples that were previously classified as NSCLC NOS (4). This shift in tumor acquisition goals and requirements, continues to reverberate in clinical lung cancer care and drug development, with, for example, the initial approval by the US Food and Drug Administration (FDA) of the immune-checkpoint, anti-programmed death-ligand 1 (PD-1) inhibitor, nivolumab, for advanced squamous cell lung cancer (5).

The need for adequate tissue for the diagnosis and management of NSCLC has increased substantially over the last decade, as new anti-cancer therapies have begun to explore vulnerabilities in the genomic underpinnings of cancer. Cancer is a heterogeneous group of diseases that lead to invasion and metastasis, induction angiogenesis, replicative immortality, resistance to cell death, reprogramming of energy metabolism, evasion of immune surveillance, circumvention of growth suppressors, and sustained proliferative signaling (6). The latter is especially prevalent in subgroups of NSCLC, since sustained proliferative signaling is usually derived from genomic mutations in key oncogenes that encode for activated tyrosine kinases.

Three main genomic events lead to the direct activation of tyrosine kinases in NSCLC: overexpression or amplification (due to increased copy numbers of a certain oncogene), mutation (due to point mutations or insertions/deletions), and rearrangement with partner genes (by preserving or activating the kinase domain of oncogenes). The most prevalent oncogenes that are amplified, mutated or rearranged in NSCLCs are listed in *Table 1* (7-9).

Tyrosine kinase inhibitors (TKIs), small molecules that can block the function of kinases, have been developed as precision therapies in NSCLC. As of mid-2015, EGFR and ALK mutations are the most prevalent, clinically relevant driver oncogenes in NSCLC care. First generation reversible EGFR TKIs (gefitinib and erlotinib) and second generation irreversible EGFR TKIs (afatinib) have been shown in multiple randomized phase III trials to be superior to standard platinum-doublet chemotherapies in the first line treatment of advanced EGFR mutant lung adenocarcinomas and are FDA approved for use in this setting (10-13). In addition, novel third generation covalent EGFR TKIs that are more specific to the most common first/second generation TKI resistance mutation (EGFR-T790M) are active and have FDA 'breakthrough' review designation.

ALK mutations in lung adenocarcinomas occur through gene rearrangements (the most common partner is EML4) that lead to constitutive activation of the tyrosine kinase domain of ALK. The multitargeted ALK/MET/ROS1 TKI crizotinib led to significant responses in phase I and II trials of ALK rearranged lung adenocarcinoma, and phase III randomized trials in the second line (crizotinib versus docetaxel or pemetrexed) and first line (crizotinib versus platinum-pemetrexed) setting have confirmed that crizotinib is more effective than chemotherapy for these tumors (14-17). The FDA label of crizotinib requires tumor identification of ALK rearrangement status. In addition, the second generation ALK TKI ceritinib is FDA approved for the therapy of crizotinib-resistant ALK rearranged lung adenocarcinoma and the related compound alectinib has a FDA breakthrough designation (18,19). Other TKIs have differing levels of evidence for off-label use in lung adenocarcinomas with other genotypes (*Table 1*).

To standardize the use of tissue for the ever-changing needs of molecular diagnostics in lung cancer, in 2013, IASLC, Association for Molecular Pathology (AMP), and College of American Pathologists (CAP) published minimum molecular testing guidelines for selection of lung cancer patients for EGFR and ALK TKIs that are now widely used for day-to-day medical oncology care (20). The current guidelines prioritize use of rapid single gene assays for these two driver oncogenes. However, it is becoming evident that technological advances have reached a point where comprehensive molecular profiling using a variety of next generation sequencing (NGS) platforms is feasible in routine clinical practice; with a multitude of commercial or academic vendors providing Clinical Laboratory Improvement Amendments (CLIA)-certified NGS assays that use formalin-fixed paraffin-embedded (FFPE) specimens or cytology specimens to isolate DNA and/or RNA for analyses of a targeted panel of genes to select for the most readily targetable alterations (*Table 1*) (21,22).

Therefore, the need for sufficient, high-quality tissue

Table 1 Known driver mutations in NSCLC with associated targeted therapeutics

Molecular target/driver oncogene	Prevalence (%)	US FDA-approved TKIs in 2015	US FDA-breakthrough designation TKIs in 2015	Off label use of TKIs with significant level of evidence (NCCN category 2A)	Off label use of TKIs with lesser levels of evidence
Adenocarcinoma					
KRAS mutations	25-30	None	None	None	None
EGFR mutations	15-20	Erlotinib, afatinib	AZD9291, rociletinib	N/A	N/A
ALK rearrangements	3-7	Crizotinib, ceritinib	Alectinib	N/A	N/A
ROS1 rearrangements	2-4	None	Crizotinib	Crizotinib	Cabozantinib
MET exon 14 skipping mutation	2-4	None	None	None	Crizotinib
ERBB2 mutations	1-3	None	None	None	Afatinib
BRAF mutations (V600E)	1-3	None	Dafrafenib, dafrafenib + trametinib	Dafrafenib, vemurafenib	N/A
RET rearrangements	1-2	None	None	None	Cabozantinib
MET amplification	1-2	None	None	Crizotinib	N/A
MAP2K1 mutations	1	None	None	None	None
NTRK1 rearrangements	<1	None	None	None	None
FGFR2/3/4 rearrangements	<1	None	None	None	None
Squamous cell carcinoma					
FGFR1 amplifications	15-20	None	None	None	None
FGFR2/3/4 mutations/ rearrangements	5-10	None	None	None	None
PI3KCA mutations	5-10	None	None	None	None
DDR2 mutations	1-5	None	None	None	Dasatinib

NSCLC, non-small-cell lung cancer; FDA, Food and Drug Administration; TKIs, tyrosine kinase inhibitors; N/A, non-applicable.

material for diagnosis, staging, and treatment selection has grown significantly, concurrently with the expansion of minimally-invasive tissue acquisition methods. We will address current minimally invasive methods for tissue acquisition in the diagnosis and management of patients with lung cancer, their performance characteristics, and consider current gaps in patient care in different practice environments.

Minimally invasive techniques for tissue acquisition

Prompt and accurate diagnosis and staging of patients with lung cancer should be sought through an efficient process: one that minimizes the number of procedures before initiating treatment. Ideally, the preferred initial procedure would be able to simultaneously provide tissue for diagnosis, tumor classification, molecular testing, as well as provide staging information. However, this may or may not be possible depending on the individual patient and the need for sufficient and appropriate tissue for current and future cytological, immunohistochemical, and molecular studies. The available techniques are: mediastinoscopy, endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA), endoscopic ultrasound (EUS) with fine needle aspiration (FNA), traditional bronchoscopic TBNA and computed-tomography guided core needle biopsy (CT-CNB) or CT-FNA. The overall performance measures of these different techniques are summarized in *Table 2*.

Table 2 Non-invasive and minimally-invasive staging modalities for non-small cell lung carcinoma*

Procedure	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Number of studies	Number of specimens	Cancer prevalence (%)
CT	55	81	58	83	43	7,368	30
Integrated PET-CT	62	90	63	90	19	2,014	22
Mediastinoscopy^	81	100	100	91	35	10,648	34
TBNA	78	100	100	77	27	2,408	81
EUS-FNA	89	100	100	86	26	2,443	58
EBUS-TBNA	89	100	100	91	26	2,756	58
EBUS-TBNA + EUS-FNA	91	100	100	96	7	811	33

*, median data values, compiled from the most recent 3rd edition ACCP Guidelines for the Diagnosis and Management of Lung Cancer [Silvestri *et al.* (23)]. PPV, positive predictive value; NPV, negative predictive value; PET-CT, positron emission tomography-computed tomography; TBNA, transbronchial needle aspiration; EUS-FNA, endoscopic ultrasound guided fine needle aspiration; EBUS-TBNA, endobronchial ultrasound with transbronchial needle aspiration; ^, includes traditional mediastinoscopy and video-assisted mediastinoscopy.

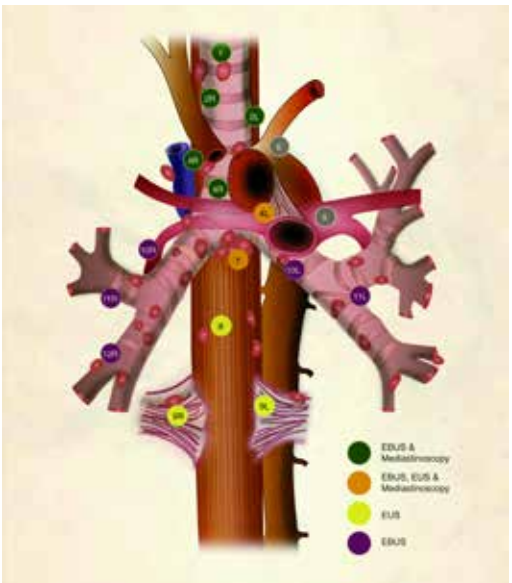

Figure 1 Lymph node map adapted from the 2009 IASLC lung cancer staging project. The lymph node stations are color coded to indicate the minimally-invasive staging techniques that can readily access each lymph node station. The close proximity to vascular structures highlights the importance of direct visualization or ultrasound guidance to avoid bleeding complications. EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; IASLC, International Association for the Study of Lung Cancer.

Mediastinoscopy

Mediastinoscopy is a surgical procedure that allows for the exploration of the superior mediastinum from the sternal notch to the subcarinal space and sometimes can reach the main bronchi (*Figure 1*). It is done under general anesthesia, with the neck maximally extended and through a 2-3 cm collar incision at the sternal notch carried out through the platysma. The strap muscles are separated to expose the trachea and after incising the pretracheal fascia, the pretracheal plane is developed. Finger dissection is initially used as caudally as possible while palpating key structures such as the innominate artery and the aortic arch. This space is then used to advance the video-mediastinoscope. This process is continued by using suction/coagulation device sweeps to advance caudally. Before carrying out biopsies, the surgeon identifies the innominate artery, aortic arch, pulmonary artery and the azygos vein. Occasionally, the appearance of a lymph node and a vascular structure are similar, and a fine needle is used to gently penetrate the structure and identify if there is blood flow or not (24).

In a similar fashion to EBUS or EUS, exploration of the lymph nodes starts on the contralateral side of the tumor to rule out N3 disease and then proceeds in a systematic way. The subcarinal lymph nodes are usually sampled last because bronchial artery and perinodal bleeding can be more difficult to control. It is important to mention that by convention the specificity and positive predictive values of cervical mediastinoscopy are considered 100%, as entire lymph nodes are excised for histologic evaluation. However, positive results are not confirmed by other tests. The median sensitivity of conventional mediastinoscopy is reported to be 78% with a median negative predictive value of 91% (23). Video-mediastinoscopy has a median

sensitivity of 89% with a negative predictive value of 92%. Although rare, complications occur in 3% of cases with serious bleeding in 0.4% occasionally requiring mediastinotomy (25,26). Mortality is under 0.5% (27,28).

There are two technical variations of mediastinoscopy intended for systematic removal of mediastinal lymph nodes: video-assisted mediastinoscopic lymphadenectomy (VAMLA) and transcervical extended mediastinal lymphadenectomy (TEMLA). These two procedures, also called "supermediastinoscopies", are not widely used but their exceptional operating characteristics warrant a comment. Both are done through an incision similar to the one used for mediastinoscopy but with systematic removal of the lymph nodes. In VAMLA, the removal of subcarinal and right inferior paratracheal lymph nodes en block followed by the left inferior paratracheal lymph nodes is done through a 2-blade spreadable mediastinoscope (29).

In TEMLA, a sternal retractor elevates the sternum allowing for complete mediastinal lymphadenectomy from the supraclavicular to the paraesophageal lymph nodes. A thoracoscope is also used to remove the subaortic and para-aortic lymph nodes (30).

Although both are rarely used, the sensitivity of VAMLA was close to 100%, while TEMLA has shown to be superior to mediastinoscopy and EBUS (31,32).

Interestingly, some experts and authors of the prior research studies, conclude that VAMLA and TEMLA have no current role in the routine mediastinal staging of lung cancer. In part due to their invasiveness and high risk of complications when compared to equally accurate but less invasive options including EBUS and EUS (33). Furthermore, VAMLA and TEMLA are not mentioned (23) or recommended only within clinical trials (34) in the most recent guidelines for staging of lung cancer.

Endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA)

Endoscopic techniques have emerged as the procedure of choice for diagnosis and staging of lung cancer (23). These techniques have also been associated with lower morbidity and mortality, and have been suggested to be more cost effective than mediastinoscopy (35,36). Complications are very rare, with the rate of pneumothorax between 0.07% and 0.2% (37). The procedure is usually done in the outpatient setting by pulmonologists, interventional pulmonologists, or thoracic surgeons in a procedure suite or in the operating room. Anesthesia largely depends on local practices, but may involve moderate sedation or general anesthesia. A dedicated flexible bronchoscope with an ultrasound (5, 7.5, 10 and 12 MHz) at the distal end is inserted through the mouth, an endotracheal tube, or a laryngeal mask and advanced to the distal trachea where apposition of the ultrasound probe to the airway wall reveals adjacent structures in high detail. After identifying the lymph node station based on anatomic landmarks, a 21 or 22 gauge needle is advanced under direct visualization on ultrasound.

Although there is no consensus on the number of times each lymph node is punctured (passes), in our experience, three passes with 15 needle excursions per pass provides diagnostic material in over 95% of cases (38). After each pass, the needle is withdrawn and a small amount of material can be either placed on a slide for immediate preparation or the entire sample can be placed in a preservative solution for cytologic analysis and cellblock preparation. As shown in *Figure 1*, EBUS can access the following stations: 2R and 2L (upper paratracheal), 4R and 4L (lower paratracheal), 7 (subcarinal), 10R and 10L (hilar), 11R and 11L (interlobar), on occasion 12R and 12L (lobar) as well as paratracheal and parabronchial masses that occur close to the airway. At least one case series that encompasses multiple institutions described access to station 5 (subaortic) through a transpulmonary artery route (39).

Endoscopic ultrasound guided fine needle aspiration (EUS-FNA)

EUS is also a real-time ultrasound procedure guiding trans-esophageal needle aspiration. It allows posterior mediastinal sampling through the esophageal wall. The lymph nodes preferentially accessible to EUS are the inferior pulmonary ligament (level 9), paraesophageal (level 8), subcarinal (level 7), and left paratracheal (level 4L) (*Figure 1*). However, anterolateral paratracheal (levels 2R, 2L, and 4R) are difficult to sample with EUS. EUS also has a high safety profile, similar to EBUS (40,41). The main feature that sets apart EUS from other techniques is the access to locations outside of the mediastinum, such as the left lobe of the liver, a significant part of the right lobe of the liver, and the left adrenal gland (42). Given its relative strengths and weaknesses, it is best to think of EUS as a complement to EBUS for the diagnosis and staging of lung cancer patients. When used in combination, the yield is higher than with either technique used alone. Pooled analyses have shown sensitivity of 91% and specificity of 100% (23,43).

CT-guided biopsy

Computed tomography provides details on the anatomic location, shape, margins, attenuation of the primary lesion as well as the extent of invasion of the chest wall, presence of suspicious mediastinal, hilar, segmental lymph nodes, and proximity to surrounding structures (44). However, this radiologic evaluation is not entirely specific and should not be used as the single source of staging. The median sensitivity and specificity of CT for identification of mediastinal lymph node involvement were 55% and 81% respectively (23). Other studies have shown similar low sensitivity when pooled in meta-analysis demonstrating sensitivity of 51%~64% for NSCLC (45,46). Whenever CT guidance is used to obtain tissue by core needle biopsy or fine needle aspiration, the pooled sensitivity and specificity are 90% and 97% respectively (47). However, the complications include a 15% risk of pneumothorax and 1% risk of major hemorrhage (48). The risk factors for major complications during trans-thoracic needle aspiration include emphysema, small lesion, greater depth of needle penetration, and multiple needle passes. For these reasons, it is not common to use trans-thoracic needle aspiration to sample mediastinal lymph nodes.

In summary, the different minimally invasive techniques are designed to help clinicians identify lung cancer patients who are likely to benefit from primary resection, neo-adjuvant chemotherapy and/or radiation, or palliative chemotherapy. However, recent studies suggest that the strategic combination of staging techniques (such as EBUS, followed, when negative, by mediastinoscopy) provides better outcomes and may be more cost-effective (49). A study by Farjah and colleagues reported severe underuse of multimodality staging; with the use of multimodality staging increasing over time from 1998 to 2005 resulting in an association between use of multimodality staging and improved survival, irrespective of the stage of disease (50).

If only imaging studies are used for staging, 15%~40% of patients will be denied curative intent therapy (51). For these reasons, radiologic images that are concerning for lung cancer or metastatic disease should be confirmed with cytology or histopathology. Inadequate lymph node evaluation is unfortunately common and its consequences are hard to estimate, but likely translates into reduced lung cancer survival if nodal disease is not identified and treated (52-54).

Lymph node mapping

Regardless of how thoracic lymph nodes are sampled for staging purposes, it is important to use a common vocabulary when describing the location of these lymph node stations as well as to state what specific lymph node stations were sampled. The Japanese (Naruke) and US/European (Mountain and Dresler) lymph node maps were reconciled into a single universal map by the IASLC in 2009 (55). This provides a uniform, specific anatomic definition of the lymph node stations, and facilitates the identification of the exact location during surgery, radiologic interpretation and minimally-invasive biopsy techniques (see Rami-Porta *et al.* in this special issue). It is recommended that we abandon loose anatomic descriptions such as "lower paratracheal" or "parahilar" as these terms are not specific to a lymph node station and can easily be misinterpreted.

Definitions for mediastinal lymph node evaluation

Using standard definitions for the thoroughness of mediastinal nodal staging is as important as using a uniform mediastinal lymph node map (56). The following categories have been used for surgical staging, but they can easily be extrapolated to minimally invasive techniques such as EBUS TBNA. The extent of lymph node assessment can be broadly categorized into the following groups (57):

(I) Random sampling: the sampling of lymph nodes by convenience or by preoperative or intraoperative findings. The most common situation is the sampling of a single enlarged lymph node. Unfortunately, this practice has been found to be very common in the mediastinoscopy literature (52).

(II) Systematic sampling: the sampling of predetermined lymph node stations, such as 2L, 4L, 7, and 10L for a left sided lung tumor, and 2R, 4R, 7 and 10R for a right sided tumor.

(III) Mediastinal lymph node dissection: the complete surgical removal of all identifiable mediastinal lymph node tissue based on anatomic landmarks.

(IV) Extended lymph node dissection: the removal of bilateral paratracheal and cervical lymph nodes by formal dissection.

(V) Lobe-specific systematic node dissection: the removal of ipsilateral mediastinal lymph node tissue based on the location of the tumor.

Guidelines on tissue acquisition and processing for diagnosis, staging, and genotyping

The American College of Chest Physicians (ACCP) evidence-

based clinical practice guidelines, the European Society of Thoracic Surgeons (ESTS) guidelines, and Cancer Care Ontario (CCO) Program in Evidence-Based Care Practice Guidelines are in agreement on their recommendations for indications and techniques for invasive staging (23,34,58). It is important to emphasize that random sampling or sampling of a single enlarged lymph node is considered inadequate surgical staging. Some authors have extrapolated this to minimally invasive techniques and have advocated against random sampling (59). It is recommended that appropriate staging include stations 2R, 2L, 4R, 4L, and 7. However, TBNA of lymph nodes that are smaller than 5 mm is very difficult and likely will result in sub-optimal amount of tissue for diagnosis. Clinically suspicious lymph nodes, such as enlarged (≥1 cm short axis diameter) or FDG-avid nodes, should also be sampled. Guidelines, such as those published by ESTS, the United Kingdom's National Institute for Health and Care Excellence, and CCO, recommend that appropriate lymph node assessment should be systematic and include a minimum of three mediastinal lymph node stations, one of which should be station 7 (subcarinal) (34,58,60).

Sample acquisition and processing differences: how does needle aspiration (cytology) differ from core biopsy (histology)?

It is important to have an appreciation for how small biopsies obtained by minimally invasive means are processed and evaluated by the pathologist/cytopathologist. In general, these small biopsy or cytology specimens must be sufficient to establish a diagnosis of malignancy, to make a reliable subclassification of disease (e.g., adenocarcinoma *vs.* squamous cell carcinoma) using immunochemical stains, and, increasingly, for molecular testing to identify targetable driver mutations. The amount of information to be gleaned from these small biopsy and cytologic specimens is great, and has increased dramatically over the past decade.

Minimally invasive biopsy specimens are small, with limited cellular material. Transbronchial/endobronchial biopsies and transthoracic core needle biopsies of lung lesions can provide some tissue architecture, helpful in delineating invasive carcinoma from in-situ/lepidic pattern of spread, though sampling limitations can be an issue for these specimens. Cytologic aspirates (EBUS-TBNA or EUS-FNA) oftentimes lack these architectural cues, though frequently larger tissue fragments that are almost biopsy-like can be aspirated and appreciated on direct smears or cell block preparations. Establishing a diagnosis of malignancy on cytologic specimens should rarely be a problem though, as the cytologic features of malignancy are generally easy to appreciate. In contrast to biopsy specimens, which are nearly always formalin-fixed and paraffin-embedded, cytologic specimens can be processed and evaluated in a number of ways, including by direct smears or touch-preparations of tissue biopsies (either air-dried or alcohol fixed), alcohol-fixed liquid based concentration methods (such as using cytospin, ThinPrep, or SurePath), as well as the creation of a tissue cell block. The latter captures the cellular material into a cell pellet that is formalin-fixed and paraffin-embedded, creating for all intents and purposes a tissue-biopsy-like specimen from which multiple serial slides can be cut from the paraffin block and used for immunohistochemical stains and molecular testing. In reality, the lines between small biopsy specimens and cytology specimens (especially with the creation of a good cell block) have become blurred, with both types of specimens capable of providing specific histopathologic diagnoses and serving as substrates for molecular testing.

In order to preserve cellular material for downstream molecular testing, the 2015 iteration of the WHO classification of lung tumors (61) and the 2011 IASLC/ATS/ERS classification of lung carcinomas on small biopsy/cytology specimens (62) recommends that a focused panel of immunostains be employed for the work-up of a suspected primary NSCLC when histology or cytomorphology alone is insufficient to distinguish adenocarcinoma from squamous cell carcinoma. Specifically, one lung adenocarcinoma marker (traditionally the transcription factor TTF-1) and one squamous cell marker (usually p63 or more recently p40—the N-terminal truncation isoform of p63 shown to be more specific for squamous cell carcinoma) (63). If these results are inconclusive, then second line lung adenocarcinoma markers (such as the aspartic proteinase Napsin-A) and squamous cell carcinoma markers (cytokeratin 5/6) can be employed. A mucicarmine histochemical stain can also be helpful to demonstrate glandular differentiation. Clinical and radiologic correlation are always helpful, to focus the immunohistochemical work-up of carcinoma metastatic to the lungs, especially when more lung-specific markers are negative.

Genotyping: yield of different techniques

The most current guidelines from the CAP, IASLC, and AMP call for testing all advanced stage lung

adenocarcinomas (or mixed tumors with an adenocarcinoma component) for EGFR mutations, generally by PCR-based methods, and ALK gene rearrangements (via FISH assay or with screening immunohistochemistry) (20). Lung cancers are also commonly tested for KRAS mutations which are associated with resistance to tyrosine kinase inhibitors. In addition to these three main molecular targets, the list of less common driver mutations (*Table 1*) in lung adenocarcinoma is growing rapidly. With the growing number of actionable targets for lung cancer, relying on the current paradigm of one-off testing using these small biopsy or cytology specimens will inevitably deplete the cellular material despite the cytopathologist's best efforts to maximize cell block cellularity and minimize material loss during the initial diagnostic work-up. Therefore, a shift towards multiplexed panels seems inevitable in future (21).

Many groups have published very good molecular testing success rates using small biopsy and cytology specimens. In general, the success rates for small biopsy specimens (including transthoracic core needle biopsies or transbronchial biopsies) are comparable to those for cytology cell block specimens. Recent studies comparing these modalities report a molecular testing success rate for small biopsy specimens of 55%~100%, and a success rate for FNA or EBUS-TBNA cell block specimens of 46%~95%, depending on the study parameters (64-67). In general there is a higher molecular testing failure rate from small biopsy or cytology specimens as compared to larger surgical resection specimens, inferred from the limiting tumor cellularity present in the former (68).

A recent publication from the Lung Cancer Mutation Consortium, a multi-institutional program investigating selected oncogene drivers in lung adenocarcinoma, revealed that in an 8-gene panel testing approach, 35% of cytology specimens and 26% of small biopsies were insufficient for molecular testing (compared to only 5% of surgical resection specimens). Importantly however, the authors comment that once a specimen was deemed adequate for molecular testing (i.e., has sufficient tumor cellularity), the specimen type (cytology/small biopsy/surgical resection) had no influence on subsequent molecular testing performance and (69) that minor differences between completion rates were not felt to be clinically significant. Therefore, cytology and small biopsy specimens have been proven to be excellent substrates for molecular testing, as long as enough tumor cells are obtained and the preceding pathologic work-up is efficient and minimized tumor cell loss.

Advanced bronchoscopy techniques in non-academic settings

EBUS-TBNA has become increasingly commonplace outside of academic medical centers. However, appropriate training for thorough and systematic mediastinal staging is still lagging (59). Electromagnetic navigation bronchoscopy (ENB), and other advanced diagnostic techniques have also become increasingly commonplace in the community setting. Each of these procedures has an associated learning curve, requiring the development of a systematic approach to proper procedural techniques for biopsies and tissue handling. Increasing interest has led to implementation of training in advanced bronchoscopy techniques in pulmonary/critical care fellowships, as well as dedicated interventional pulmonary fellowships.

For physicians who did not have exposure to these techniques during their formal training, the training options include taking a sabbatical year, participating in an intense 1-7 day course, or direct proctoring by experienced colleagues. Current ACCP guidelines for procedural training are based on minimum number of procedures and not necessarily on the cognitive and technical skills required (70). In the United States, the need for the procedures at community and regional hospitals has led to the implementation of bronchoscopy services, including EBUS, or the creation of referral channels to tertiary care centers (71). Ultimately, the success of community programs depends on adequate investment of human and technological capital, ideally within multidisciplinary teams of pulmonologists, thoracic surgeons, radiologists, cytopathologists, radiation oncologists, and medical oncologists, who should collaborate to apply evidence-based guidelines while continuously evaluating their performance using mutually accepted yield and quality metrics.

A number of authors have advocated the utility of rapid onsite examination (ROSE) for the evaluation of EBUS samples. Although immediate feedback for the bronchoscopist as well as appropriate specimen collection and triage can be helpful in certain circumstances, the current guidelines from the World Association for Bronchology and Interventional Pulmonology state that use of ROSE is not recommended for every case if the operator is experienced (72), and certainly should not limit the implementation of a much needed service for lung cancer patients. In this setting, EBUS-TBNA samples for driver oncogene mutation analysis has been successful in close to 95% of the cases, even with use of a commercial laboratory

and no sample enrichment (64). Appropriate tissue handling and preparation with methanol based fixatives and paraffin-embedded cell blocks have been used successfully by our group and others (68,73).

Conclusions

The diagnosis and treatment of lung cancer has undergone multiple dramatic changes in the last decade. We have a better understanding of the molecular biology of lung cancer and driver mutations that can be targeted through the use of specific tyrosine-kinase inhibitors. Significant technological advances allow interventional pulmonologists and surgeons to obtain diagnostic material in a safe and minimally invasive manner. Ongoing refinements in diagnostic and ancillary molecular testing by pathologists and cytopathologists has allowed small biopsy and cytology specimens to be used to accurately diagnose and characterize lung cancer, helping direct appropriate therapeutic decisions. Moving forward, a pressing task for the health care community at large will be to narrow existing practice gaps between high-performing (often academic) and lower performing (often community-based) care delivery settings.

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Footnote

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Early diagnosis of solitary pulmonary nodules

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Abstract: Early detection of solitary pulmonary nodules (SPNs) and early treatment are of great importance. However, patients with early SPNs always do not present with any symptoms or signs, only to demonstrate SPNs in radiology findings. So it is very critical to improve the ability to identify the SPNs, and with the development of sorts of diagnostic modalities, the accuracy in the evaluation of the SPNs has improved greatly. In this paper, the diagnostic methods and techniques of SPNs are reviewed.

Keywords: Solitary pulmonary nodules (SPNs); early; diagnosis

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With the development of equipment and technology, solitary pulmonary nodules (SPNs) are being increasingly detected year by year. The reported detection rate of SPNs is about 8%~51% (1). The differentiation between benign and malignant nodules, and the management thereof, has thus become the main focus of interest and challenge in clinical research nowadays. The goal is to rapidly identify the nature of a pulmonary nodule, making early detection and treatment possible, and in turn avoid unnecessary invasive examination or open-chest surgery for benign lesions. Based on the clinical experience regarding the diagnosis and treatment of SPNs in the past decade in our department, we presented the techniques and advancement in the early diagnosis of SPNs in recent years in this study, as follows.

Overview of the early diagnosis

Definition and etiology of SPNs

A SPN is an isolated, single lesion in a round or oval shape with a diameter of ≤3 cm in lung parenchyma, surrounded entirely by gas-containing lung tissue. Such lesions are not accompanied by lung atelectasis, hilar enlargement or pleural effusion (2,3) (*Figure 1*). Despite a variety of causes, SPNs are common in granulomatous diseases and lung cancer, and not often seen in carcinoid tumors or a single lung metastasis of other tumors. It is rare in hamartomas and pulmonary arteriovenous malformations (*Figure 2*).

Risk factors of lung cancer in SPNs

When a pulmonary nodule is detected, the probability of malignancy should be evaluated first. The clinical evaluation includes a review of medical history and examination of physical sign. Clinical risk factors indicating a high probability of malignancy include the size of nodule, age, history of tumor, COPD, smoking history, and history of asbestos exposure (See *Table 1*) (4).

Common non-invasive examination of SPNs

Commonly used non-invasive tests of SPNs include: sputum cell biology techniques, blood biomarker detection and imaging.

Sputum cell biology techniques

Sputum cytology is a non-invasive and simple cytological test, with a sensitivity of 28%~80% for early diagnosis of lung cancer. Due to certain restrictions, however, the

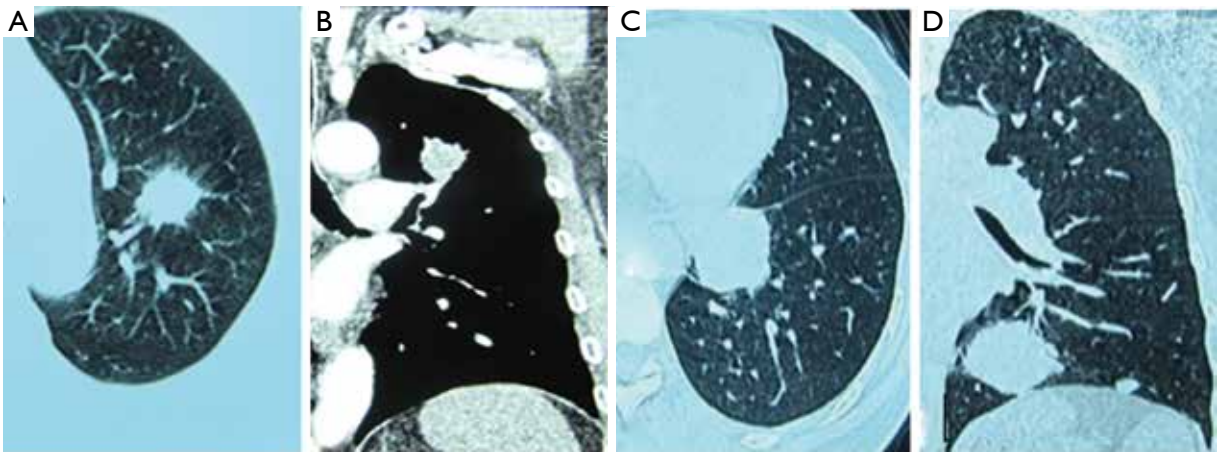

Figure 1 A and B are nodules; C and D the masses.

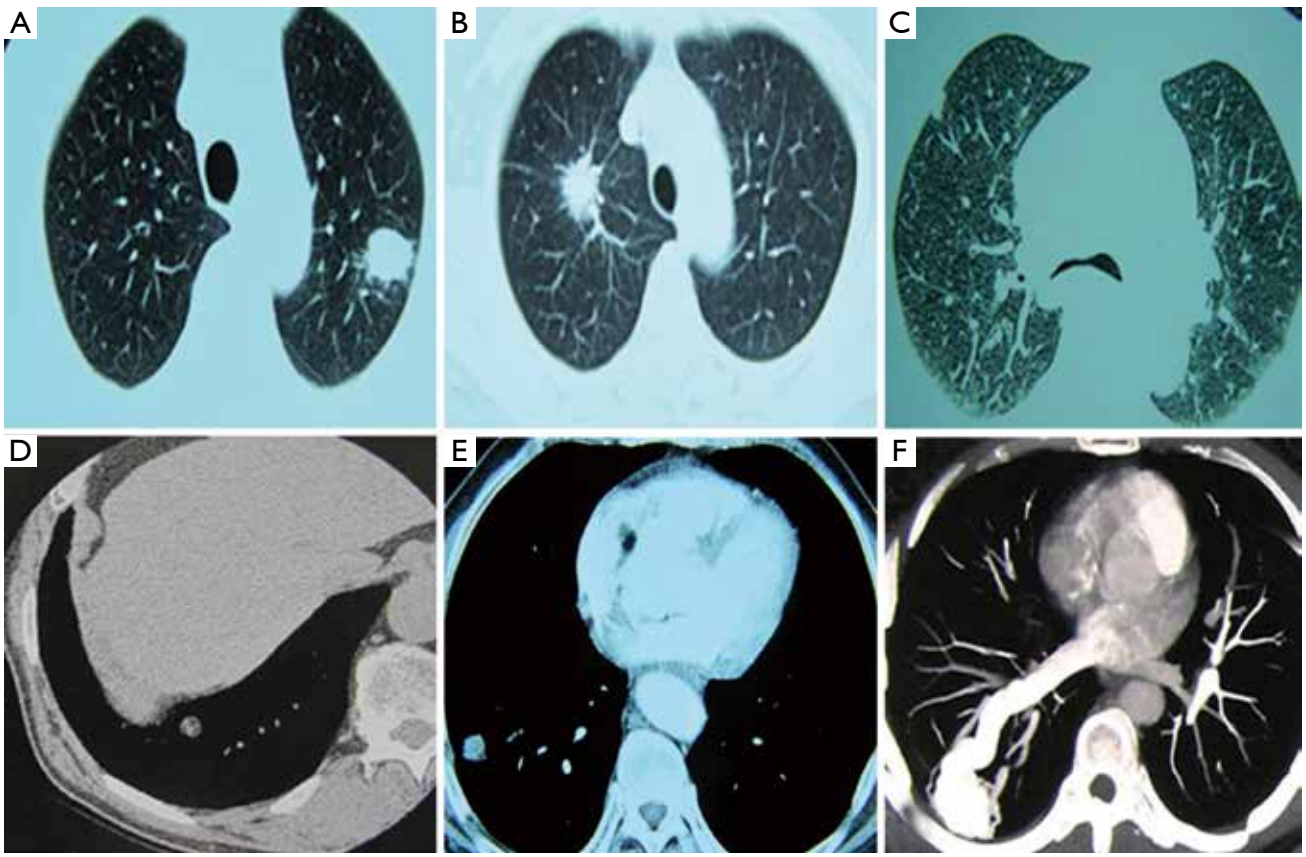

Figure 2 SPN causes: (A) tuberculoma; (B) bronchogenic cancer; (C) lung metastasis of skin cancer; (D) hamartoma; (E) carcinoid; (F) lung artery or vein abnormalities.

Table 1 Risk factors and risk of cancer in patients with SPNs

Factor	Tumor risk		
	Low	Medium	High
Nodule size (diameter in mm)	<8	8-20	>20
Age (year)	<45	45-60	>60
History of tumor	No	–	Yes
Smoking history	Never smoked	<1 pack/day	≥1 pack/day
History of smoking cessation	≥7 years after stopping smoking	<7 years after stopping smoking	Never quitted
COPD	No	Yes	–
History of asbestos exposure	No	–	Yes
Nodule characteristics	Smooth	Lobular	Burrs

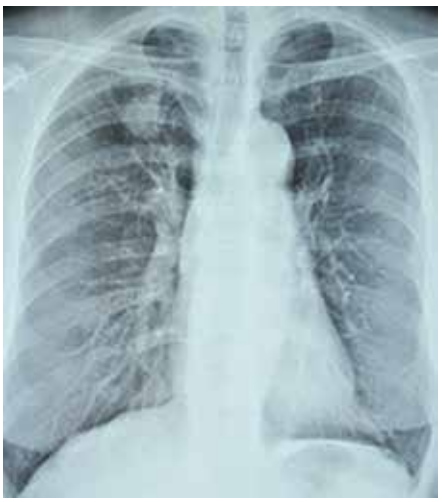

Figure 3 Chest X-ray examination reveals right upper lung nodules.

positive rate in the diagnosis of SPNs is not high. In recent years, thin liquid based cytology has been introduced, but it still can not meet the clinical demands. The detection of DNA ploidy changes in sputum cytology can help increase the early diagnosis rate of malignant pulmonary nodules.

Detection of biomarkers

These mainly include a number of tumor markers, such as carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), cytokeratin 19 fragment (Cyfra21-1), carbohydrate antigen (CA125), lung cancer-associated antigens, vascular endothelial growth factors, proliferating cell nuclear antigens and epidermal growth factor receptors, which have attracted a wide range of interests. Detecting a single marker is of limited value in the diagnosis of malignant lesions, and the combined use of multiple markers is thus preferred. It has been reported (5) that malignant SPNs have significantly elevated tumor marker values compared with benign SPNs. In cases with SPNs, serum CEA and Cyfra21-1 are highly sensitive indicators of lung cancer, and the combination of both is helpful in differentiating the benign and malignant lesions.

Imaging techniques

(I) Chest radiographs (CR) are commonly used in chest examination. Most patients are often found to have SPNs through this method. According to foreign reports, the examination pulmonary nodules rate on CR is about 0.09-0.2% (6) (*Figure 3*); (II) computed tomography (CT) is currently considered the most sensitive imaging examination of lung nodules. In particular, the introduction of multi-slice CT has greatly improved the detection rate and qualitative accuracy in the diagnosis of pulmonary nodules (*Figure 4*); (III) positron emission computed tomography (PET): PET/CT combines PET that reflects the metabolic capacity of a tumor and CT that shows the organizational structure in a high-resolution way. It has a sensitivity of 97% and a specificity of 85% to SPNs, and is recognized as the optimal non-invasive means of differentiating benign SPNs from malignant ones (7). According to most studies, the maximum standardized uptake value (SUV_{max}) of 2.5 is used as a diagnostic threshold, in which a SUV_{max} of ≥2.5 is suggestive of malignancy (*Figure 5*); Malignancies with a SUV_{max} of ≤2.5 are often bronchioloalveolar carcinoma

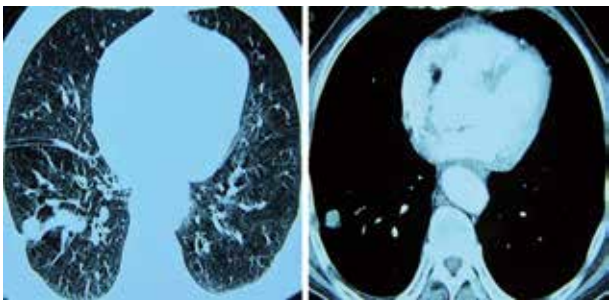

Figure 4 Multislice spiral CT shows pulmonary nodules.

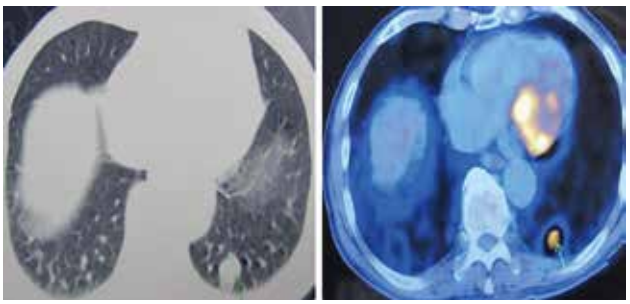

Figure 5 PET/CT shows right upper lung nodules, SUVmax =4.5.

and metastatic carcinoid tumors. For SPNs ≤1 cm in diameter, a SUV_{max} of ≥2.5 is not highly accurate in the diagnosis of malignancy. False positive results can occur in granulomatous inflammation, fungal infections, tuberculosis, or other active inflammation.

Imaging characteristics and assessment of probability of malignancy

Imaging parameters used to assess the risk of pulmonary nodules include the nodule size, margin characteristics, density, and peripheral signs.

Size

Generally, small nodules tend to be benign, while larger ones are more likely malignant (*Figure 6*). The probability of malignancy is less than 1% in nodules <4 mm; and around 0.9%, 18% and 50% in those of 4-7 mm, 8-20 mm and 20-30 mm, respectively (8). Therefore, the SPN diameter can be used as an independent risk factor for differentiating malignant and benign lesions.

Edge characteristics

The edge characteristics provide an important basis for the differentiation between benign and malignant nodules. Malignant SPNs are often associated with irregular contours, spiculated edge and increased lobes (*Figures 7,8*). In a clinical prediction model based on Logistic regression analysis, Swensen *et al.* (9) established that lobulation has a positive predictive value of 88%~94% for malignant nodules, and can be used as an independent risk factor for malignant nodules. Lindell *et al.* (10) analyzed lung cancer screening results for five years, and found margin changes

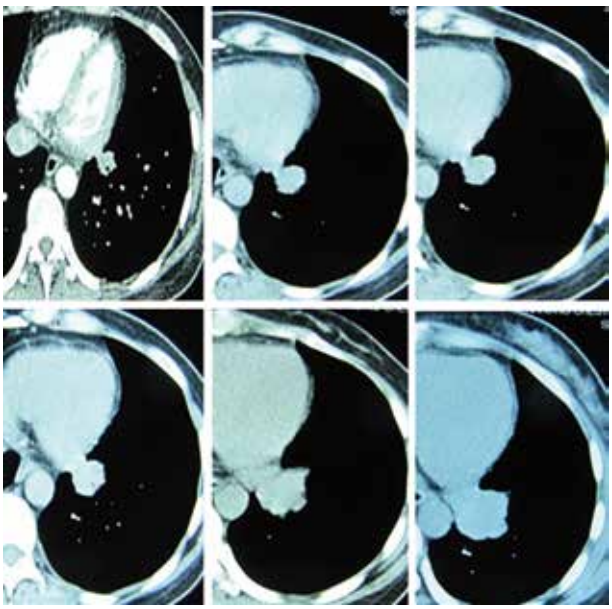

Figure 6 Nodule size changes, longest diameter 1.6-4.0 cm.

in 42% of tumors with progression, of which 80% was lobulation and increased burrs. However, nearly 25% of benign nodules have lobulated edge as well (11).

Density

Calcification is considered to be an important imaging characteristic for differentiation of malignant and benign lesions. A study reported (12) that benign and malignant SPNs accounted for 97% and 3%, respectively, in 504 patients with calcified nodules, and 29% and 71% in 1,109 patients without calcification, respectively. Popcorn-like calcification is often associated with hamartoma (*Figure 9*). Calcification is, however, still present in about 2%~13% of nodular lung cancer, 33% of carcinoid tumors and other

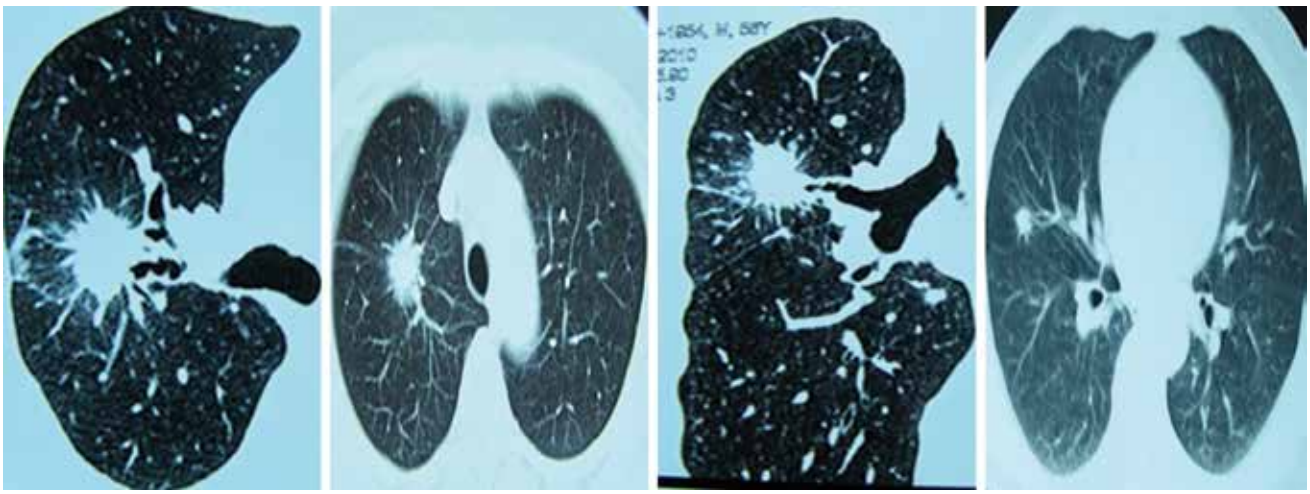

Figure 7 Burr-like nodule margins.

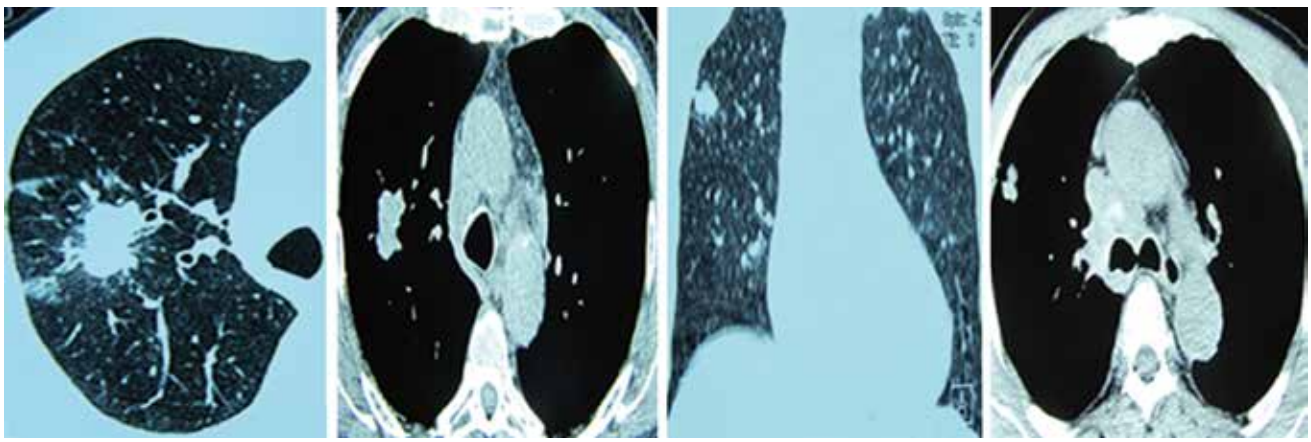

Figure 8 Lobulated nodule margins.

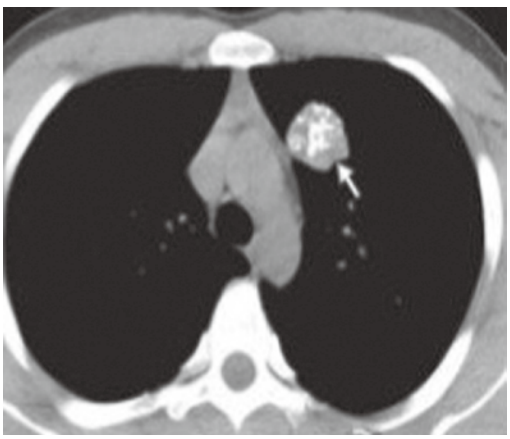

Figure 9 Popcorn-like calcification of density in lesion.

malignancies (13). Fat-containing nodules are a specific diagnostic sign of hamartoma, but can also be present in a small part of malignancies (14).

The uneven density of solid nodules is mainly reflected as the vacuole sign, air bronchogram and cavity. Vacuoles and aerated bronchioles are significantly more frequently seen in lung cancer compared with benign nodules (*Figure 10*). As reported (15), vacuoles are present in 28.7% of lung cancer in a size of <3 cm, while those ≤2 cm in diameter account for 60.4%. In contrast, only 8.5% of lesions with this sign are benign. According to the report by Kui *et al.* (16), of 132 SPN patients, 30% patients with lung cancer had aerated bronchi, while benign lesions presented only 5.9%. Lung cavities are not as often seen in small lung

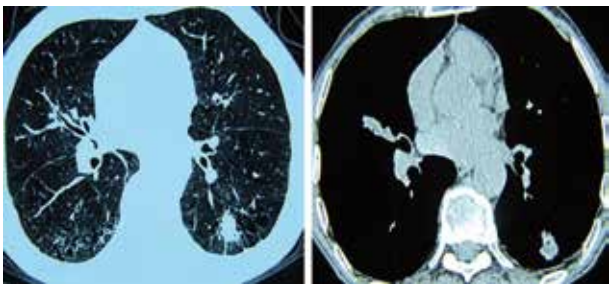

Figure 10 Uneven nodule density, reflected as the vacuole sign.

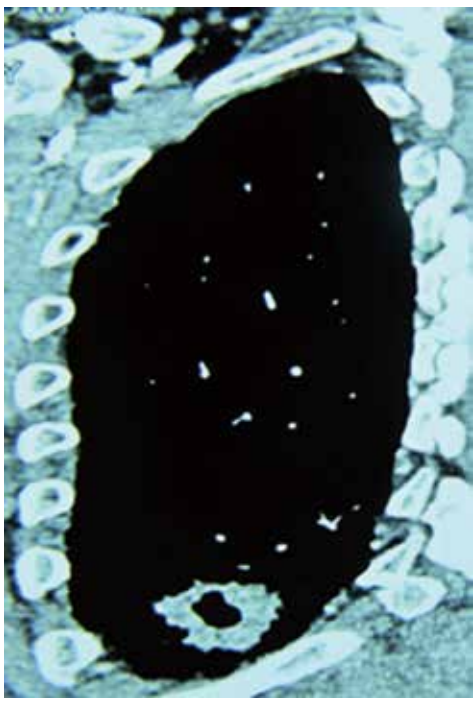

Figure 11 Eccentric cavities with uneven wall thickness.

cancer as tuberculoma. A cavity in lung cancer is mostly eccentric with uneven wall thickness (*Figure 11*).

Compared with solid nodules, ground-glass opacities (GGOs) or semi-solid pulmonary nodules are more likely malignant. According to a report (17), 75% GGOs are bronchioloalveolar carcinoma or adenocarcinoma with bronchioloalveolar carcinoma as the primary component, 6% atypical adenomatous hyperplasia, and approximately 19% benign lesions (*Figure 12*).

Peripheral signs

The vessel convergence sign is often seen in peripheral lung

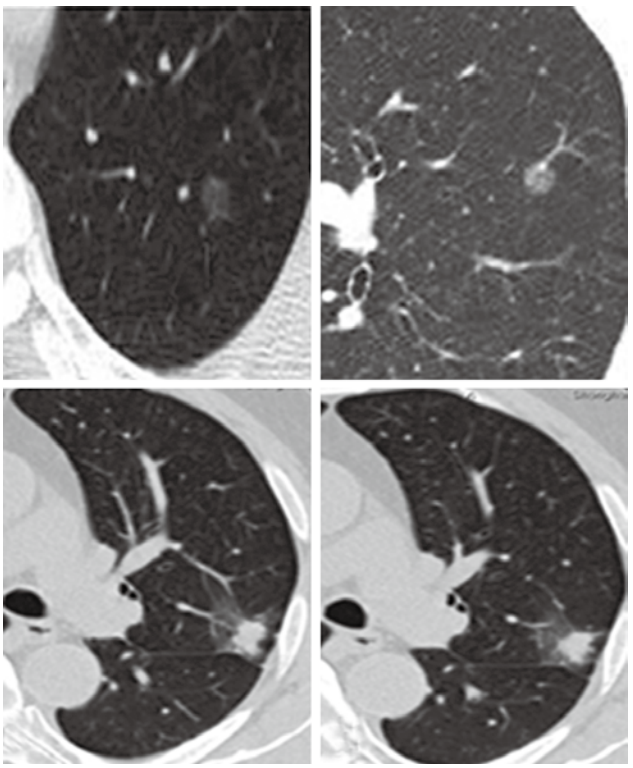

Figure 12 A and B are pure ground-glass nodules; C and D semi-solid nodules.

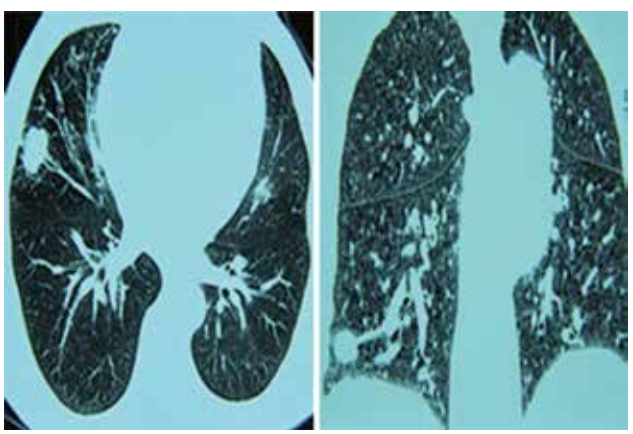

Figure 13 Vascular convergence sign of the periphery of lesion.

cancer (18), and in 83%~94.8% malignant SPNs (*Figure 13*). Pleural indentation is present in 49% lung cancer, all of which are peripheral lung cancer, mostly adenocarcinoma and alveolar cell carcinoma (19) (*Figure 14*). Satellite lesions around a SPN are commonly indicative of granulomatous inflammation in the lung (*Figure 15*).

Growth rate

The growth rate of nodules is commonly evaluated with the volume doubling time. If a lesion grows significantly in volume, it tends to be malignancy and often has a doubling time of about 30-400 days (20). Those with a doubling time longer than 400 days are often benign tumors or granulomatous inflammation due to pulmonary infections (21) (*Figure 16*).

Minimally invasive techniques for early diagnosis in medical departments

Medical minimally invasive techniques for the early diagnosis of SPNs include: fiber optic bronchoscopy (FOB), percutaneous lung biopsy or needle aspiration biopsy, and medical thoracoscopy (*Table 2*).

Fiber optic bronchoscopy (FOB)

FOB-based pathological techniques for the diagnosis of SPNs include bronchial brush cytology (BB), bronchial alveolar lavage (BAL) and transbronchial lung biopsy (TBLB) (*Figure 17*). When a SPN is ≤2 cm in diameter, especially located in the outer 1/3 field of the lungs, its diagnostic accuracy is merely 14% (22). The development of endobronchial ultrasound, ultrathin bronchoscopy and electromagnetic navigation has improved the sensitivity of TBLB.

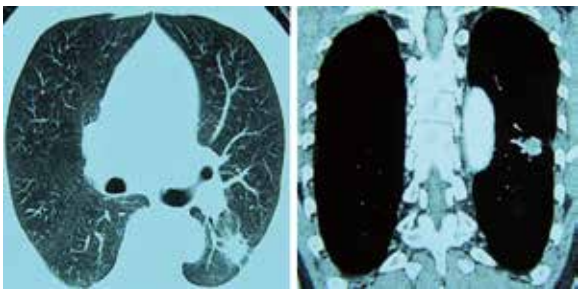

Figure 14 Pleural indentation of the periphery of lesion.

Endobronchial ultrasonography (EBUS)

Sends the ultrasound probe into the tracheal and bronchial lumens through bronchoscope, and achieves the images through real-time ultrasound scanning of the trachea, bronchial wall layers and surrounding organs and vessels. It can be used to identify the abnormal changes of submucosal, wall and peripheral airway lesions and locate peripheral lesions (*Figure 18*). Depending on the ultrasound probe type, EBUS can be divided into radial probes (RPs) and convex probes (CPs). RP-EBUS has a smaller diameter, and thus can be put through the bronchoscope to the target area, which is mainly used to examine peripheral lesions, but can not be used for lesion biopsies under real-time monitoring. CP-EBUS combines ultrasound probe and the distal end of the endoscope, enabling lesion biopsies under real-time monitoring with significantly improved accuracy and safety of the puncture. It is mainly used for observations and biopsies of large airway walls and the surrounding lesions. According to a report (23), transbronchial biopsy using endobronchial ultrasonography with a guide sheath (TBLB-EBUS-GS) has a diagnosis rate of 77% for peripheral lung lesions and, in particular, 74% for those with a diameter ≤3 cm.

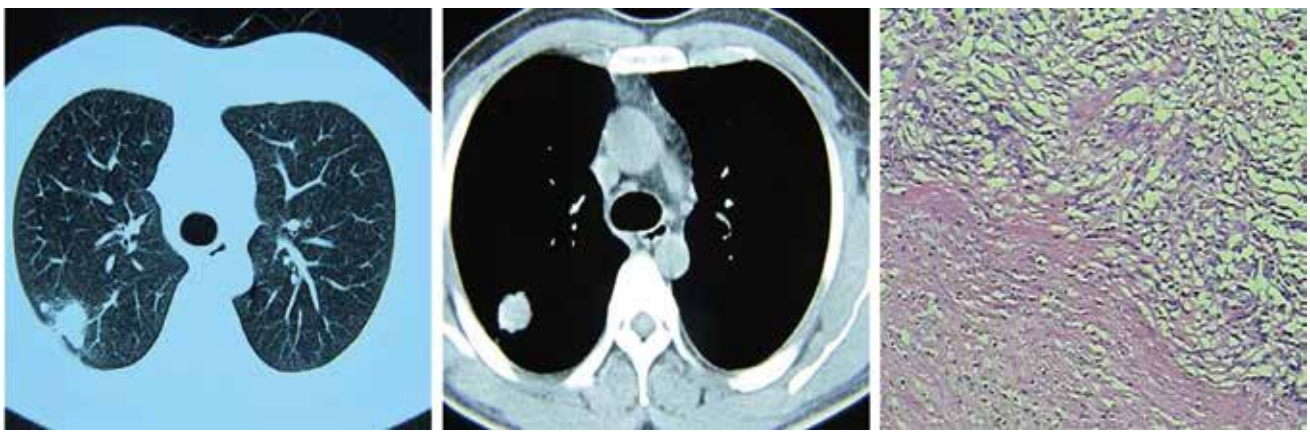

Figure 15 Satellite lesions of the periphery (HE ×400).

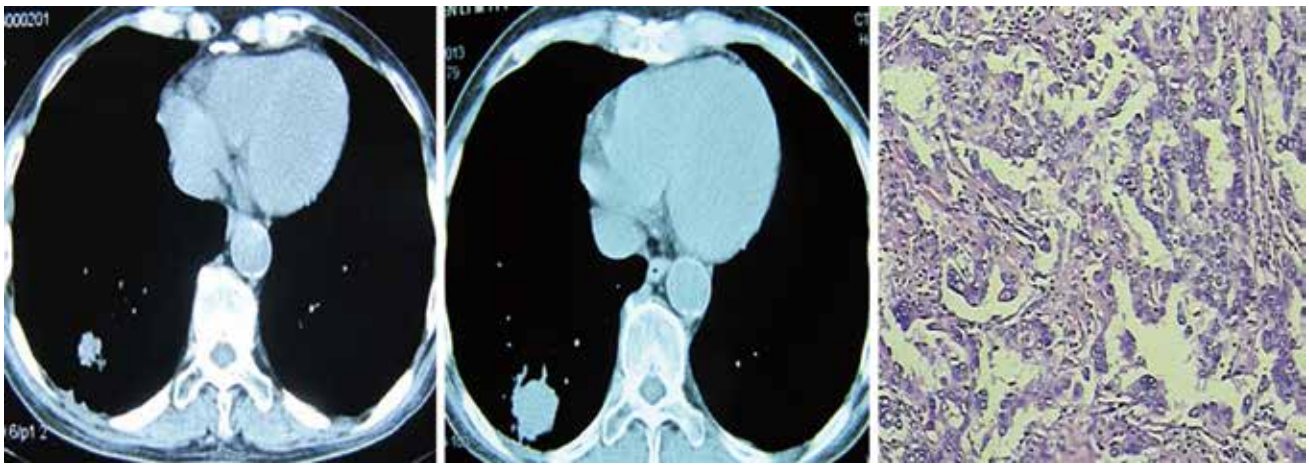

Figure 16 Right lower lung nodules (2013-03-13), progressing into tumor (2013-9-16), and pathologically confirmed as lung adenocarcinoma (HE ×400).

Table 2 Characteristics of minimally invasive techniques in medical departments

Medical minimally invasive techniques	Clinical evaluation	Advantages
Endobronchial ultrasonography	(I) Reveals the layers of the airway wall and the organizational structure outside the airway wall; (II) Helps in determining the nature of peripheral lung lesions; (III) Serves as a guidance in the biopsy or brush cytology of peripheral lung lesions	Small nodules around the bronchi; peripheral lung nodules
Electromagnetic navigation bronchoscopy	(I) Can be used for the diagnosis of peripheral lung nodules, without the need of X-ray imaging; (II) Is accurate, safe and well tolerated in the diagnosis of early peripheral lesions; (III) Can be used in biopsies of mediastinal lymph nodes	Small peripheral lung lesions; mediastinal and hilar lymph node biopsies
Ultrathin bronchoscopy	(I) Can reach 6 to 8 level bronchioles, making it easy to detect lesions in small endobronchial locations, and enabling biopsies and brush cytology under direct vision; (II) Reaches peripheral lesions accurately under the X-ray guidance, providing multiple-site biopsies for central or peripheral lesions	Peripheral lung lesions; lesions in the upper apices, posterior segments and lower lobes of the lungs
Percutaneous lung biopsies or aspiration biopsies	(I) Provides accurate positioning, with a low incidence of complications and a high positive rate; (II) Yields cytological and histological specimens	Peripheral pulmonary lesions
Medical thoracoscopy	(I) Enables minimally invasive, least painful and easy-to-operate examination or treatment within a short period of time; (II) Enables biopsies of lesions, providing adequate specimens and high positive rates	Diagnosis of pleural diseases and treatment of pleural adhesions; small nodules on pulmonary surfaces

Yamada *et al.* (24) reported that TBLB-EBUS-GS had a diagnosis rate of 67% for peripheral lung nodules, and proposed that, to maximize the diagnostic accuracy, at least five biopsies should be carried out. Apparently, EBUS has significantly improved the diagnosis level of peripheral lung nodules.

Electromagnetic navigation bronchoscopy (ENB)

Integrates ENB to empower three-dimensional spiral CT image reconstruction and labeling. With combination of the obtained 3D simulated images and the bronchoscopic images, guidance is achieved through observation of the orientation of catheters with electromagnetic positioning sensors at the top so that the catheters can reach the specified position in the lungs for biopsies. It has been reported (25) that ENB has a diagnosis rate of 67% for peripheral lung lesions.

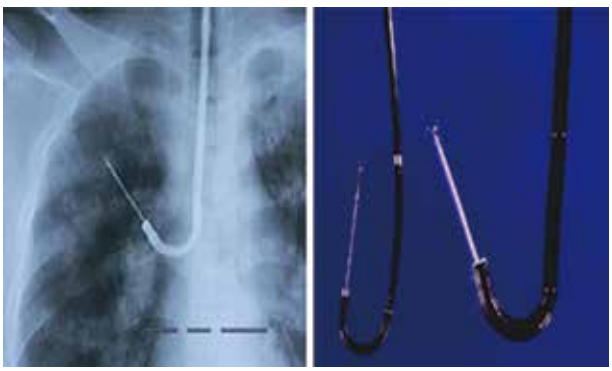

Figure 17 Transbronchial lung biopsy.

Ultrathin bronchoscopy (UB)

Refers to bronchoscopes with an outer diameter of less than 3.0 mm, UB diameter of up to 1.8 mm and biopsy pipeline of 1.2 mm. In theory, they are able to reach into the peripheral bronchi. UB is a powerful tool for the diagnosis of peripheral lung lesions, particularly under the effective guidance of a navigation system. As UB plays its superior performance when inserted into the specific locations, it can not only detect peripheral lesions in the distal ends of the bronchial tree, but also collect the specimens, which improve the diagnostic capacity of peripheral lung lesions (*Figure 19*). Yamamoto *et al.* (26) suggested in a study that UB could be an effective supplementary option to conventional bronchoscopy for the diagnosis of peripheral lung lesions. They also pointed out that, for lesions in the upper apices, posterior segments and lower lobes of the lungs, UB could be considered as the preferred examination.

Fine-needle aspiration biopsy (FNAB)

FNAB is a common method for lung tissue biopsies in clinical settings, particularly for SPNs located close to the chest wall. The mainstream needles include aspiration needles and cutting needles (*Figure 20*). Both can be used to obtain cytological and histological specimens. While those obtained by the former are smaller, incomplete and easily crushed, which may compromise the pathological findings, those with the latter type are more complete and useful for observing changes in the organizational structure. CT has a high spatial and density resolution,

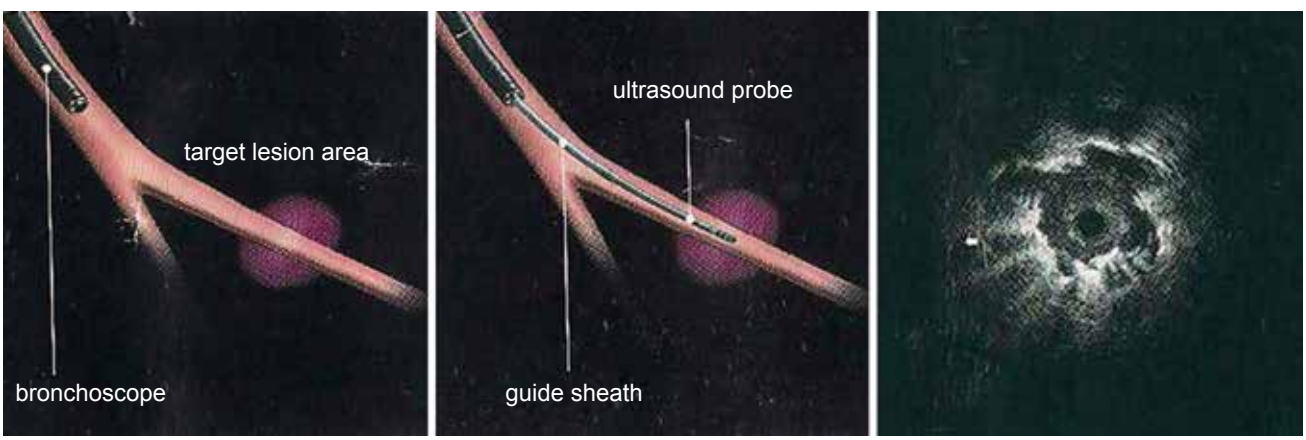

Figure 18 Ultrasound bronchoscope.

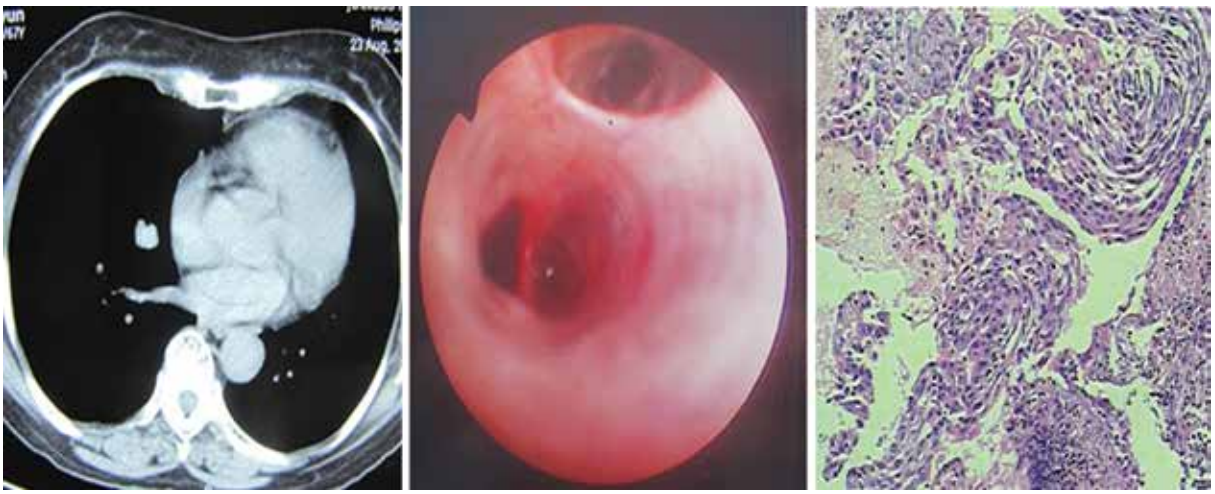

Figure 19 Ultrathin bronchoscopy reveals a lung lesion in the 4B branch of the right lateral segment, which is squamous cell carcinoma as confirmed by biopsies (HE ×400).

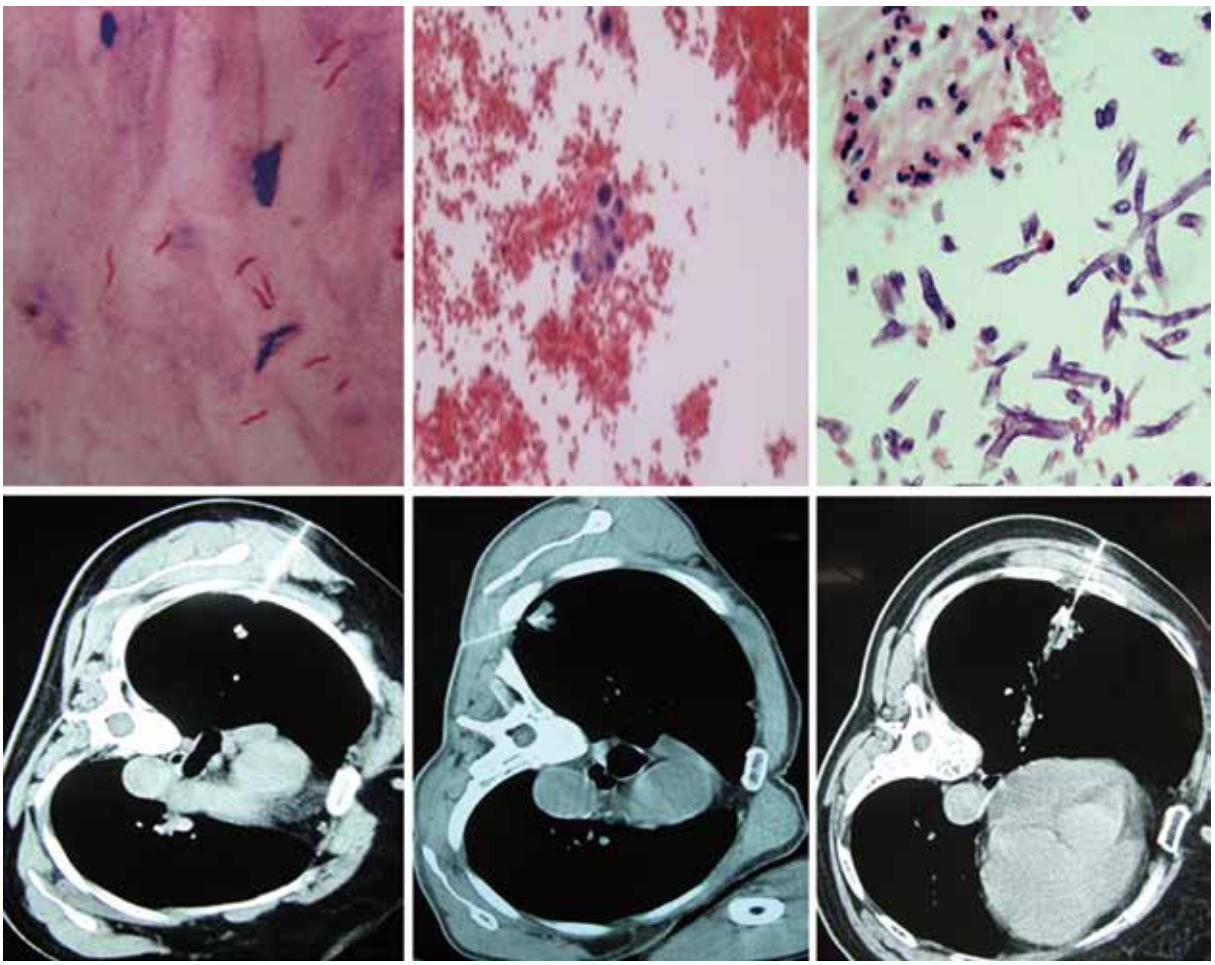

Figure 20 CT-guided percutaneous needle biopsy and needle aspiration biopsy (HE ×400).

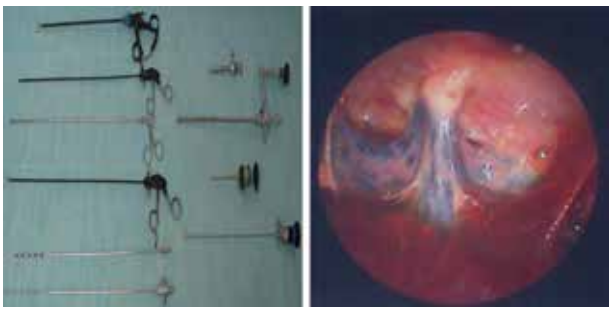

Figure 21 Biopsy of lung surface nodules under medical thoracoscopy.

and clearly shows the lesion size, density, location and the spatial relationship between the lesion and surrounding organs, which facilitates the selection of the optimal puncture site, measurement of the distance and angle of the site relative to the lesion, thereby greatly improving the accuracy of the puncture. In particular, CT guidance has its unique value for smaller lesions. A meta-analysis (27) reports that FNAB diagnosis has a sensitivity of 86% and specificity of 98.8% for malignant SPNs, while combination with CT-guided puncture will add up to a sensitivity of 91% and specificity of 94% (28). The diagnostic accuracy mainly depends on the operator's positioning and puncturing skills, in addition to the pathology technical level that may have a certain impact on the results. The main contraindications of FNAB are: severe pulmonary congestion or hyperemia; severe airway obstruction; severe cardiopulmonary dysfunction; severe coagulation disorders or active large hemoptysis; suspected vascular lesions, such as vascular malformations and aneurysm; inability to maintain a constant position for long; and inability to hold breath or be cooperative in surgery. The complications of FNAB include pneumothorax, hemoptysis, needle tract seeding of tumors and air embolism in other organs.

Medical thoracoscopy

Medical thoracoscopy, as opposed to video-assisted thoracoscopic surgery (VATS), is operated by physicians of the respiratory department in the endoscopy room, which enables minimally invasive, least painful, and easy-to-operate examination or treatment within a short period of time (*Figure 21*). It is mainly used for the diagnosis of pleural disease and treatment of pleural adhesions, and has certain value for examinations of unexplained peripheral lung lesions, as it is helpful in obtaining large parenchymal biopsy specimens. Attention should be paid to follow the indications strictly. Closed chest cavity due to pleural adhesions and pulmonary hypertension, honeycomb lung and vascular tumors during lung biopsies are absolute contraindications; severe cough, hypoxemia, coagulopathy and severe heart diseases are relative contraindications.

Video-assisted thoracoscopic surgery (VATS)

Following the above methods, when the diagnosis is still inconclusive and the imaging findings clearly suggest malignant SPNs, VATS inspection can be considered if there is no contraindication. VATS is advantageous in its minimally invasive nature, adequate exposure, image clarity, fewer complications and low mortality, and is thus an ideal method for the diagnosis and management of SPNs (29). To address the challenges for SPN diagnosis and management and intraoperative positioning particularly in deep lung lesions, <1 cm nodules, and GGO under VATS at present, such techniques have been reported (30) as anatomical positioning, technology imaging, CT guided catheter Hook Wire positioning, methylene blue injection, and intraoperative ultrasound positioning. In the case of difficulties in applying VATS treatment, diagnostic surgical thoracotomy can be performed.

In short, SPNs are still one of the challenges for clinical diagnosis and treatment of pulmonary lesions. With the increasing development of imaging, ultrasound and bronchoscopic techniques, the diagnosis and treatment levels of SPN will be greatly improved. The combination of biomarkers and other means will be a trend of development in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

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Noninvasive computed tomography-guided marking technique for peripheral pulmonary nodules

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Background: Identification of the exact location of small peripheral pulmonary nodules during thoracoscopic wedge resection (TWR) is crucial. We describe a new method of computed tomography (CT)-guided marking without puncturing the visceral pleura (VP) for minimally palpable pulmonary nodules.

Methods: Preoperative CT scans were performed 1 day before TWR with the patient in the lateral decubitus position. Under CT guidance, we marked the skin over the pulmonary nodule. During TS, an indwelling catheter was inserted perpendicular to the marked skin surface and put a mark with gentian violet (Pyoktanin blue®, Wako Pure Chemical Industries, Osaka, Japan) onto the VP. We palpated the nodules near the mark(s) and performed TWR.

Results: Between October 2012 and April 2016, we performed CT-guided marking in 54 patients (24 males and 30 females, median age 65 years). Cases included 39 primary lung cancers, 10 metastatic lung tumors, and 5 benign tumors. The mean diameter of the nodules was 10 mm (range, 3–26 mm), and the mean distance of the nodule from the VP was 4 mm (range, 0–17 mm). The mean time of intraoperative marking was 3.5 min (range, 1–4.5 min). The mean distance from the nodule to the marking point was 7.0 mm (range, 0–30 mm). We were able to identify the location of the nodule using this procedure in 53 patients (98%). Hematoma of the chest wall after marking was observed in one patient. There were no other complications.

Conclusions: This marking technique is a simple, economic, and effective procedure to locate small peripheral pulmonary nodules during TWR.

Keywords: Thoracoscopic surgery; computed tomography (CT); solitary pulmonary nodule; multiple pulmonary nodules

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Introduction

Peripheral small pulmonary nodules such as ground glass opacities (GGO) and possible lung metastases require a tissue diagnosis. Minimally invasive thoracoscopic wedge resection (TWR) is a good therapeutic option for these peripheral pulmonary nodules. However, in some cases, it is difficult to identify the exact location of a small peripheral, but not subpleural, nodule during TWR. In such cases, preoperative marking is often employed (1-5). Although preoperative CT-guided marking techniques are the most common, most of them require puncture of the visceral pleura (VP). CT-guided hookwire placement before resection has been performed, but is subject to complications such as pneumothorax, hemothorax, and air embolism from puncture of the VP (6,7). A CT-guided marking technique that does not puncture the VP is less prone to these complications. We developed and performed a marking technique using CT guidance that does not involve VP puncture, based on the report of Nishida *et al.* (8).

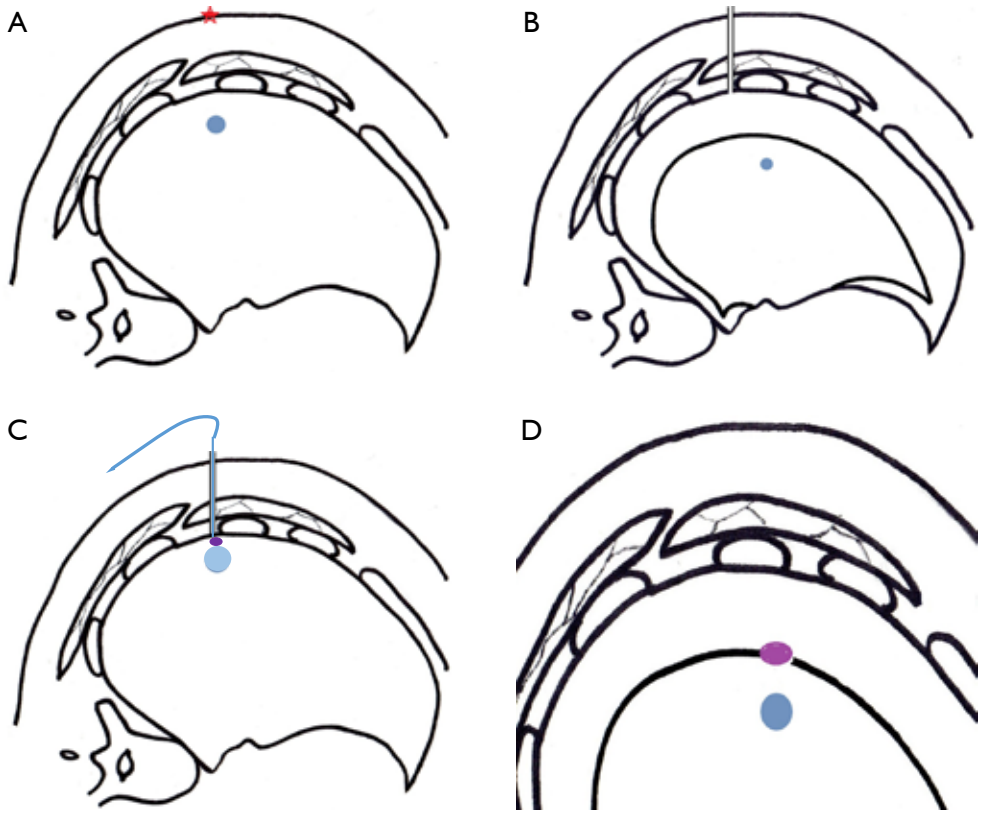

Figure 1 Technique of noninvasive CT-guided marking. (A) A skin mark representing the shortest distance to the pulmonary nodule; (B) under single ventilation, an indwelling catheter was inserted vertically from the skin mark through the chest wall and into the thoracic cavity; (C) after inflation of the lung, gentian violet pigment was stamped using an epidural catheter; (D) the visceral pleura was pigmented near the pulmonary nodule.

Methods

This study was an exploratory, single-armed study approved by the ethics committee of our institution (No. 1114), and written informed consent was obtained from each patient. The indication for marking was a histologically undiagnosed peripheral pulmonary nodule or nodules ≤20 mm in diameter designated for TWR. Fifty-four patients were enrolled in this study from October 2012 to April 2016.

Technique

Our hospital is a referral center, so the patients had undergone initial CT scanning at other institutions. Patients with small peripheral pulmonary nodules are generally followed for at least 3 months using thin-section CT (TSCT). TWR is reserved for nodules. Preoperative CT scans were performed 1 day before the operation. Patients were placed in the lateral decubitus position to best approximate their position during TWR, using radiopaque markers on the body surface. Scans were acquired in the maximal expiratory phase. A mark was placed on the patient's skin at the shortest distance from the nodule (*Figure 1A*). At operation, patients received general anesthesia and were placed in the lateral decubitus position with the side to be operated uppermost. After the relevant lung was collapsed and the thoracic cavity was entered though either one or two trocar ports, a 16-gauge indwelling catheter (Surflo®, Terumo Corporation, Tokyo, Japan) was inserted perpendicular to the skin surface through the chest wall at the mark and into the thoracic cavity (*Figure 1B*). The needle was removed and the external catheter hub was fixed to the thoracic wall. After reinflating the lung, a φ 1.0 mm epidural catheter (Hakko Medical, Tokyo, Japan) containing gentian violet dye was inserted through the indwelling catheter. The tip of the catheter touched and tattooed the VP of the inflated lung (*Figure 1C*), which was identifiable

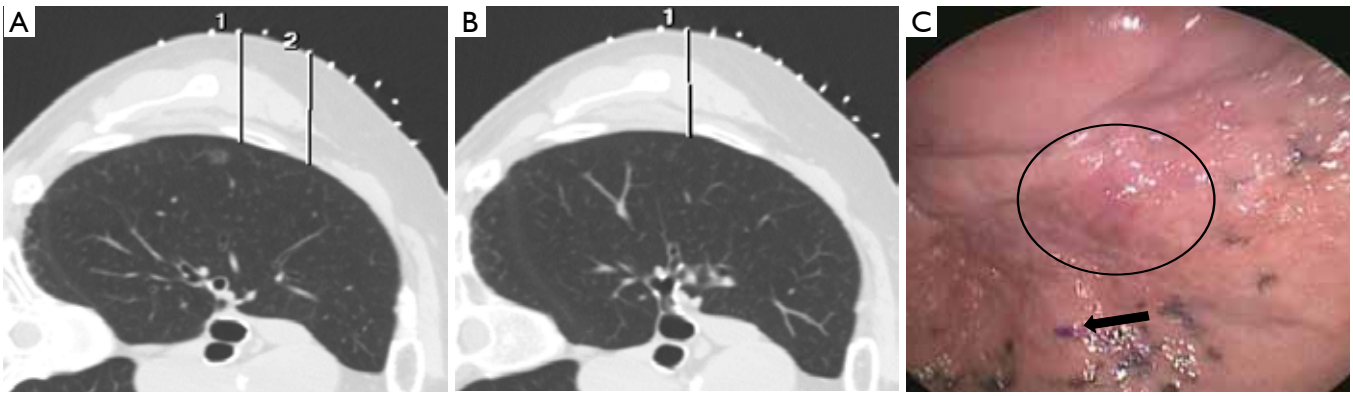

Figure 2 Procedure of 1-point method. (A) A small pure ground glass nodule was located in right upper lobe; (B) skin mark was set 2.5 mm below the nodule to avoid the rib; (C) the visceral pleura was pigmented with gentian violet (bow) near the nodule (circle).

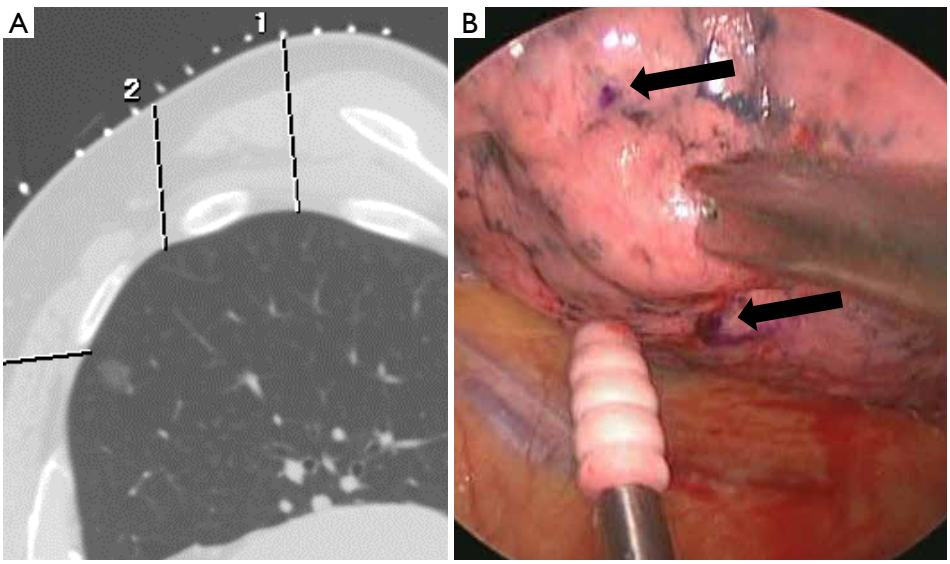

Figure 3 Procedure of 2 points method. (A) Pulmonary nodule is located beneath the rib. Two skin marks were placed at the same axial line; (B) two marks were observed on the visceral pleura (two bows). Target nodule could be palpated on the line extending to these two points.

after deflation of the lung (*Figure 1D*). We usually palpated around the marking point using endoscopic instruments and fingers through the port site, and then TWR was performed using endoscopic staplers.

During the preoperative CT, we usually put one mark on the VP for one pulmonary nodule (one-point method, *Figure 2*). However, if the nodule was located beneath the scapula or ribs, the shortest distance to the nodule may not be a straight vertical line. In such situations, we performed a two-point method. Two marks were placed on the patient's skin in the same axial plane in the CT examination and the VP tattooing followed. During the operation, the two tattoo points were identified, and we palpated the nodule along the line connecting these two points (*Figure 3*).

Results

Patient characteristics are shown in *Table 1*. In this study, ground-glass nodules (GGNs) on preoperative TSCT findings were observed in forty patients (74%). Cases included 39 primary lung cancers, 10 metastatic lung tumors, and 5 benign tumors. The mean tumor size was 10 mm (range, 3–20 mm) and the mean distance of the tumor from the VP was 4 mm (range, 0–17 mm). The one-point method

Table 1 Patient characteristics

Characteristics	(N=54)
Gender (male/female)	24/30
Age, years*	65 [36–78]
Preoperative CT findings (GGN/solid)	40/14
Tumor size, mm**	10 [3–20]
Distance from visceral pleura, mm**	4 (0–17)
Body mass index, kg/m^2	22.5 (17.6–30.3)
Thickness of chest wall, mm*	34 [6–80]
Histology	
Primary lung cancer/metastatic tumor/benign	39/10/5
Marking points (one/two)	41/13
Intraoperative marking time, min**	3.5 (1–4.5)
Distance from the nodule to the marking point, mm**	7.0 (0–30)
Complication***	1 (1.8%)

*, values are presented as median (range); **, values are presented as mean (range); ***, hematoma of chest wall. CT, computed tomography; GGN, ground glass nodule.

was performed in 41 patients and the two-point method was performed in 13 patients. The mean distance from the nodule to the marking point was 7.0 mm (rage, 0–30 mm). The mean intraoperative marking time was 3.5 min (range, 1–4.5 min). Complications of this procedure were seen in one patient, who developed a hematoma of the chest wall because of injury to an intercostal artery. We could not detect a nodule in one patient because of insufficient collapse of the lung. In the other 53 patients (98%), we detected the nodules and performed successful TWR.

Discussion

Indications for surgical resection of small pulmonary nodules have been increasing due to recent advancements in CT screening. TWR is a minimally invasive approach to obtain a pathologic diagnosis and may be curative. However, sometimes the target nodule is not readily palpable and time is required to detect it. Preoperative marking allows quick intraoperative identification.

There are two preoperative marking techniques, CT-guided and bronchoscope-guided (3,8). In CT-guided marking technique, percutaneous hookwire placement is the most common procedure (4,5). Hookwire placement is relatively easy for nodule localization. However, puncture of the VP is an associated hazard that may result in complications such as air embolism (6,7). Similar techniques using insertion of pigment or contrast media may carry the same risk because of puncture of the VP. To avoid these complications, several marking techniques without VP puncture have been reported (8,9). We already reported the efficacy and feasibility of CT-guided nodule marking in 2015 (10). Compared with contrast media, gentian violet is easy to see with the naked eye, obviating the need for exposure of radiation during surgery.

Bronchoscope-guided marking techniques can also be performed without puncturing the VP (3,11). However, these marking techniques need both expensive equipment and expert skills. In addition, these techniques are more painful and invasive than CT-guided techniques. Preoperative marking techniques for peripheral pulmonary nodules require a balance among accuracy, technical ease, and minimal invasiveness.

In our experience, NICTM has two limitations. One is that there is no information on the depth of the nodule from the VP. For nodules located >30 mm from the VP, thoracoscopic segmentectomy is necessary to obtain appropriate surgical margins. The other limitation involves the inflation of the lung before tattooing the VP. In this study, we missed one nodule during surgery because of the marking was slipped off from the nodule. We have been waiting >1 minute after inflating the lung to achieve full expansion before tattooing. In addition, sufficient collapse of the lung is important to palpate nodules after marking, requiring close collaboration with the anesthesiologist.

Conclusions

Noninvasive CT-guided marking without puncturing the VP is a feasible and effective procedure to localize peripheral pulmonary nodules prior to TWR.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was an exploratory, single-

armed study approved by the ethics committee of our institution (No. 1114), and written informed consent was obtained from each patient.

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Towards optimal pathologic staging of resectable non-small cell lung cancer

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Abstract: Pathologic nodal staging is the most accurate means of determining prognosis of patients with resectable non-small cell lung cancer (NSCLC), but confusion prevails about the optimal pre-operative and surgical lymph node examination procedures for candidates of curative-intent resection. The landmark American College of Surgeons Oncology Group Z0030 trial revealed no difference in the survival of patients with clinical T1 or T2, N0 or N1 (hilar node-negative), M0 NSCLC who either had a fastidious, pre-defined systematic hilar and mediastinal lymph node sampling procedure, or who received a complete mediastinal lymph node dissection. We place the results of this major trial into a contemporary clinical practice context, and discuss problems associated with apparent misunderstanding of the lessons from this trial, especially in light of evidence of prevailing sub-optimal nodal examination practices. We also discuss evolving knowledge about the origin of the quality gap in pathologic nodal staging and the emerging literature on corrective interventions.

KeyWords: Lymph node examination; quality improvement; surgery; survival

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Accurate staging is essential to the appropriate treatment of cancer. After histologic confirmation of a diagnosis of lung cancer come the questions: 'what is the prognosis?', 'what are the best treatment options?', 'how likely is treatment to be successful?', 'will chemotherapy be necessary?' The answer to each of these questions requires knowledge of the stage of the cancer. The tumor, node, and metastasis (TNM) system, our current means of staging lung cancer, serves many functions. It is the language with which we communicate the extent of a patient's cancer across time and space, provides prognostic information, guides selection among treatment alternatives, and is a key aspect in selecting patients for clinical trials.

Advances in technology have improved the accuracy of clinical staging. Clinical staging incorporates all non-invasive radiologic tests such as computerized tomography (CT), positron emission tomography (PET), magnetic resonance imaging, and bone scans (1,2). In the surgical resection population, in which distant metastasis has usually been ruled out, the most difficult staging problem is the accurate determination of nodal metastasis status. Radiologic determination of the size and extent of the primary tumor is fairly accurate, although delineating the T3-T4 border, i.e., determining whether a tumor that seems to extend to major mediastinal structures is actually invasive (T4) or merely abutting (T3), can sometimes only be resolved at thoracotomy. However, nodal status is the most important determinant of survival in the lung cancer patient who does not have distant metastatic disease, and the question of lymph node metastasis is less easily resolved by radiologic tests (1,3). Invasive clinical staging of mediastinal lymph nodes may be accomplished by transbronchial needle aspiration, endobronchial ultrasound guidance, endoscopic ultrasound guidance, mediastinoscopy, video-assisted mediastinal lymphadenectomy, transcervical extended mediastinal lymphadenectomy or video-assisted

Table 1 Comparison of 5-year survival rates by clinical and pathologic staging in the International Association for the Study of Lung Cancer staging project cohort. Modified from ref (12)

	5-year survival rate (%)	
	AJCC 6	AJCC 7
IA		
Clinical	50	50
Pathologic	73	73
IB		
Clinical	40	43
Pathologic	54	58
IIA		
Clinical	24	36
Pathologic	48	46
IIB		
Clinical	25	25
Pathologic	38	36
IIIA		
Clinical	18	19
Pathologic	25	24

thoracoscopy (2,4,5).

However, clinical staging tests have their sensitivity, specificity and accuracy limitations. The positive predictive value (PPV) for CT ranges from 0.16 to 0.88 and the negative predictive value (NPV) ranges from 0.54-0.83 (1). Specifically, normal sized lymph nodes by CT criteria may harbor metastatic disease and enlarged lymph nodes may be enlarged because of benign processes such as postobstructive pneumonia, histoplasmosis, and sarcoidosis. The likelihood of an enlarged mediastinal node being histologically positive is only 60% whereas 20% of normal sized nodes may harbor metastasis (6). Similarly, PET-positive nodes may have increased metabolic activity because of an inflammatory process whereas histologically positive nodes may be negative on PET because of low metabolic activity or low burden of disease. Although PET performs better than CT, with a PPV ranging from 0.40 to 1.00 and a NPV ranging from 0.71-1.00, the false-negative rate is approximately 20% for normal sized nodes. Conversely, enlarged nodes that are PET positive are falsely positive 15%~25% of the time (1). Invasive tests have limits imposed by the reach of the instrument and the degree of effort applied by the operator, or what Frank Detterbeck has described as the 'thoroughness of execution' (7).

Recent studies have demonstrated the value of combining clinical staging tests in the pre-operative work up of patients (8,9). For this reason current staging guidelines, including Cancer Care Ontario's Program in Evidence Based Care Practice Guidelines, recommend invasive mediastinal staging in the presence of either enlarged nodes on CT or "hot" nodes on PET to rule out false-positive imaging tests. These guidelines also recommend invasive mediastinal staging even with a negative CT and PET for high risk tumors (defined as central, large, T3/T4, or adenocarcinoma) (10).

For all the advances in clinical staging options, the most accurate determination of stage in patients who are able to undergo surgical resection comes from examination of the resection material obtained at thoracotomy (pathologic staging) (11). Comparison of the 5-year survival rates in groups of patients who are staged by clinical and pathologic means reveals a 5%~23% higher survival in patients with pathologic stage I, II, and IIIA over those with the identical clinical stage (*Table 1*) (12). This difference is independent of the combination of descriptors used to assign aggregate stage, and is probably partly explained by the 'Will Rogers phenomenon', in which improved staging accuracy leads to more accurate assignment of low risk patients into low risk groups and upstaging of seemingly low risk patients with subtle metastatic disease into higher risk categories, thereby improving the aggregate outcomes of the higher risk cohorts (13). Pathologic staging is therefore our most accurate prognostic tool in lung cancer.

However, current pathologic staging of lung cancer remains insufficiently discriminatory of future patient outcomes. For example, the 5-year survival of patients with resected stage IA non-small cell lung cancer (NSCLC) is 73%, meaning the mortality rate of the lowest risk cohort is 27% (*Table 1*) (12). Although lymph node metastasis is our most powerful prognostic determinant in the surgical resection population, the 5-year survival of patients with pathologic N0 NSCLC is 56%, meaning that 44% of patients with apparently low risk disease die within 5 years (14). Are these poor results solely due to the biologic aggressiveness of lung cancer (or the frailty of the lung cancer patient), or do they reflect other problems such as limitations of the TNM staging system as a prognostic tool, or, very importantly-because of the opportunity for corrective intervention-poor application of the prognostic tool?

Determining the stage-relevant characteristics of the primary tumor (its size and extent of direct invasion) is relatively straightforward for the pathologist. In the surgical resection population, distant metastasis usually

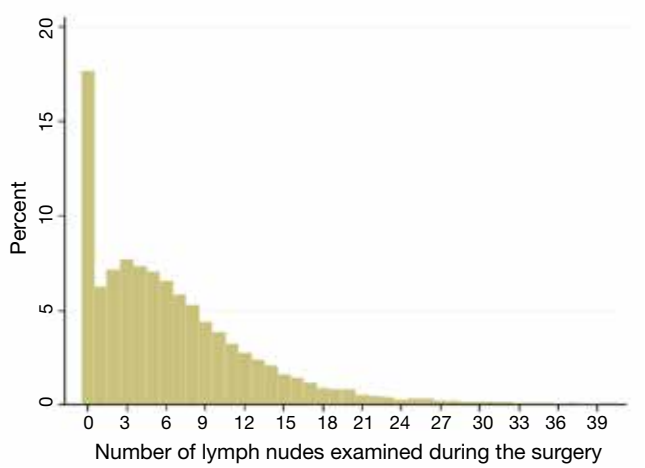

Figure 1 Number of lymph nodes examined after surgical resection of 'lymph node negative' non-small cell lung cancer. US Surveillance, Epidemiology and End Results Database 1998 to 2009. Obtained from ref (15).

being inevident, the most important pathologic staging problem is determining lymph node metastasis status. This requires the collaborative efforts of the surgeon (to retrieve the hilar and mediastinal lymph nodes, and to accurately communicate the provenance of all lymph node specimens to the pathologist for accurate mapping) and the pathologist (to examine all lymph nodes in the resection specimen, both those directly provided by the surgeon and those indirectly provided within the lung resection material). There is compelling evidence that this collaborative effort frequently breaks down, to the detriment of patients.

At one extreme, 13% of all curative-intent resections (and 18% of resections for 'node-negative disease') have no lymph nodes examined (15). The survival of patients with pathologically ambiguous nodal stage (pNX) approximates very closely to that of patients with pN1, not pN0 disease (when pN0 is defined as actually having at least one examined lymph node), suggesting that a significant proportion have missed lymph node metastasis (15). Secondly, 40%~50% of all curative lung cancer resections in large North American databases have no mediastinal lymph nodes examined (16,17). Indeed, 63% of resections for mediastinal node negative (pN0 or pN1) disease in the US Surveillance, Epidemiology, and End Results (SEER) database from 1998 to 2009 had no mediastinal lymph nodes examined, leading to a 14% survival deficit (17). To put this survival impact in perspective, the estimated absolute survival benefit of post-operative adjuvant chemotherapy is about 5.4% (18). This problem is not unique to the US (19).

Furthermore, and more subtly, most patients with pathologic N0 disease cluster at the low end of the total lymph node number spectrum, with a median lymph node count of 6 in the US (*Figure 1*) (20). Patients with fewer than 6 lymph nodes have a significantly worse survival than matched patients with greater than 6 lymph nodes despite ostensibly having the same pathologic stage (21,22). Hence the recommendation in the 7th edition of the AJCC/UICC staging guidelines for examination of at least 6 lymph nodes and 3 nodal stations (23). However, this recommendation is probably insufficiently stringent because of evidence of sequential improvement in survival of patients with pathologic N0 disease with increasing number of lymph nodes examined, with the optimal number being 'greater than 10' and possibly as high as 18 to 21 (20,24-26). It is therefore unsettling that fewer than 15% of all pN0 lung cancer resections in large US databases have examination of greater than 10 lymph nodes. Even in patients with lymph node metastasis, there is prognostic value to the number of lymph nodes examined, both in helping determine the absolute number of lymph nodes with metastasis and in determining the ratio of positive and negative lymph nodes (27-32).

The etiology of suboptimal nodal examination has been the subject of recent investigation. Conceptually, it appears reasonable to separate the origin of the problem into three sites: events during the surgical operation (such as the hilar and mediastinal lymph node harvest), events during the transfer of specimens from the operating room to the pathology laboratory, and events during the pathology examination. Clearly, when surgeons do not harvest hilar and mediastinal lymph nodes, pathologists have no access to material for a thorough staging examination. Therefore, the solution to the problem of non-examination of mediastinal lymph nodes might be best achieved by focusing on intraoperative events. However, surgeons frequently complain that the specimens they submit are not completely examined. This assertion may be supported by 'before and after' intervention studies in which use of pre-labeled specimen collection kits improves the quality of pathologic staging, with a reversion to pre-intervention levels during the intervention phase in cases when the kit is inadvertently unavailable (33).

It therefore seems plausible that the communication between surgeons and pathologists during the transfer of specimens needs to be improved. Solutions might range from prevention of specimen loss in transit (34), to

improved labeling of specimens in order to improve the ability of pathologists to determine the source and nature of submitted materials (35). Both of these factors (loss of specimens in transit, and inadequate specimen labeling) may impair the pathologic examination and lymph node mapping. The foregoing notwithstanding, the gross dissection of lung resection specimens for intrapulmonary lymph nodes may be an opportunity for pathology-centered quality improvement (36). For example, 10% of patients with one or more lymph nodes examined have no N1 lymph nodes, meaning that but for the mediastinal lymph nodes provided by the surgeon, there would have been no nodes examined in the resection specimen (37). Pathologists not infrequently omit the pathologic nodal stage in the report summary, or make errors in stage attribution, such as labeling N1 disease as N2 and vice-versa. This combination occurred in 33% of pathology reports in one city-wide audit of lung resection pathology reports (38). The very existence of the 12%~18% pNX population is the clearest illustration of the possibility of concurrent glitches in intraoperative and pathology processes.

All of this naturally raises the question: what is the optimal surgical resection and pathologic staging procedure? We shall not engage the debate about the extent of resection and whether, or not, sublobar resection is oncologically sound in lobectomy candidates, a topic that remains the subject of ongoing clinical trials in North America (Cancer and Leukemia Group B 140503, clinicaltrials.gov #00499330) and Japan (Japan Clinical Oncology Group 0802/West Japan Oncology Group 4607L); Nor shall we address the looming controversy about the appropriateness of lobar resection in patients with low grade lesions such as adenocarcinoma in-situ, minimally invasive adenocarcinoma and ground glass opacity (39); Nor shall we discuss the definition of an oncologically complete resection for lung cancer, a topic of much interest which has been provocatively addressed in the recent past (40). Our focus is primarily on the lymph node staging problem.

The optimal surgical lymph node staging procedure has been partially clarified by the landmark American College of Surgery Oncology Group Z0030 trial which compared the long-term survival of patients with clinical T1-2, N0-1 NSCLC who underwent a fastidious, pre-specified systematic sampling procedure versus a more extensive mediastinal nodal dissection (41). Although 4% of patients in the extensive dissection arm had lymph node metastasis that had been missed by the systematic sampling procedure, there was no difference in recurrence free- or overall survival between the two groups. Early data analyses from this trial established the safety of mediastinal lymph node dissection in both academic and community care settings (42). It also revealed that surgeons' attention to the mediastinal lymph node harvest procedure provides a much higher lymph node yield than usually obtained—a median of 18 additional lymph nodes were collected in the mediastinal lymph node dissection arm (two-thirds of which were N2 lymph nodes), 6 or more nodes were examined from a minimum of 3 nodal stations in >99% of patients, and a minimum of 10 lymph nodes were examined from at least 3 nodal stations in 90% of patients (43). Most importantly, ACOSOG Z0030 definitively established the adequacy of systematic sampling as an oncologically sound mediastinal lymph node staging procedure in patients with relatively low risk early stage NSCLC and is now oft-cited in support of a pathologic staging strategy short of formal mediastinal nodal dissection (44).

However, it is important that we interpret Z0030 in the right context. First, the eligibility criteria specifically excluded patients with cT3 and T4 tumors, and those with hilar or mediastinal lymph node metastasis on frozen section analysis of the lymph nodes collected after the rigorous systematic nodal sampling procedure. Therefore, the results of this trial must not be misinterpreted as proof of equivalency between the two nodal dissection procedures in higher risk patients, such as those with clinically more advanced disease, because the results may be dissimilar in these patients. Secondly, this trial cannot be cited in support of the idea that noninvasive staging (with CT and PET) is a substitute for surgical mediastinal lymph node staging. It must be emphasized that all patients in Z0030 received a fastidious nodal sampling procedure, which included sampling of lymph nodes from stations 2R, 4R, 7 and 10R for right-sided tumors and stations 5, 6, 7 and 10L for left sided tumors regardless of lymph node size or metabolic activity. The randomization to cessation of further nodal dissection versus complete mediastinal lymph node dissection was performed only after establishment of histologic node negativity in stations 2-10, and the survival analysis included only patients who met the stringent quality criteria for the nodal sampling procedure. Z0030 cannot be used to justify a strategy of either no mediastinal nodal sampling (which is the experience of a large proportion of patients who undergo resection in US databases) (16,17) or random sampling (the experience of the vast majority of all others) (45).

A prior study by Wu *et al.* corroborates the veracity

of the above observations (46). In this study, 532 patients with clinical stage I, II or III NSCLC were randomized to either mediastinal lymph node dissection or to a nodal sampling procedure that was much less thorough than Z0030, requiring hilar nodal dissection, routine harvesting of station 7 and inspection of stations 1-9 with only removal of 'nodes with suspected cancer metastasis (diameter >1 cm or hard)'. They reported improved survival in favor of node dissection with a median survival of 43 months compared to 32 months for sampling (P=0.0001). In contrast to Z0030, patients had no cytological or histological assessment of lymph nodes prior to randomization and resection, suggesting that if pre-resection systematic lymph node sampling has not been performed, survival is improved by mediastinal lymph node dissection (46).

In one community-based series, only 8% of patients who had lung resection over the course of a 4-year time span met criteria for a less stringent definition of systematic sampling than was performed in Z0030 (45). This study highlighted the loose use of terminology by surgeons: in the 45% of resections in which the surgeon reported having performed a 'mediastinal lymph node dissection', objective review of the pathology report suggested that none met the Z0030 mediastinal nodal dissection criteria, 9% were better classified as systematic sampling, 50% had random sampling and 42% had no mediastinal lymph nodes examined. It would be an unfortunate misunderstanding of the state of the evidence for the results of Z0030 to be used to justify such practice.

A less obvious side-bar to the discordance between surgeon procedure claims and the results of pathology report-based audits of the quality of nodal examination is the contribution of pathology practice. Despite the consensus statement that pathologists should 'examine all lymph nodes in the lung resection specimen' (47), re-examination of lung resection specimens after completion of routine pathology examination reveals that 137% more intrapulmonary lymph nodes (and 165% more lymph nodes with metastasis) can be retrieved from discarded lung specimens than the number retrieved during the routine examination (36). Indeed, up to 12% of patients said to have pN0 disease on routine examination, had identifiable lymph node metastasis by hematoxylin and eosin staining of discarded lymph nodes. Using fastidious intrapulmonary nodal retrieval procedures, a median of 11 N1 lymph nodes were retrieved from lobar lung resection specimens, up from a pre-intervention median of 3 N1 nodes (36). Interestingly, this is greater than the median of 5 to 6 N1 lymph nodes examined in the ACOSOG Z0030 trial, even though per study protocol surgeons helped retrieve nodes from stations 10-13 (43). This suggests that the opportunity for quality improvement in routine pathology examination of lung resection specimens exists across different types of institutions. This opportunity might be greater in routine practice because of the expectation most surgeons have that nodes within the resection specimen would be retrieved by gross dissection in the pathology laboratory.

It is incumbent on the surgeon to provide adequate N2 nodes through systematic sampling or mediastinal lymph node dissection, but also to harvest N1 nodes including stations 10 and 11. Recent data demonstrated significant upstaging with respect to N1 nodes in open compared to VATS lobectomy suggesting that surgeons were not harvesting the hilar zone nodes when performing VATS lobectomy (48). Clearly, the pathologist cannot examine nodes that are left in the chest. Optimal pathologic nodal staging requires the collaborative actions of surgeons, members of the operating room team, specimen handlers, the pathology laboratory team and the pathologist. A chain of actions is required for optimal pathologic staging of curatively resected lung cancer. Like all chains, it is only as strong as its weakest link. Effective interventions to correct the prevailing quality deficit in staging must encompass the full spectrum of potential sites of quality breakdown, from the surgical operation to the posting of the final pathology report.

Interventions in which pre-labeled specimen collection kits have been combined with fastidious gross dissection of the lung resection specimen demonstrate early promise in rectifying the quality deficit. Studies of these interventions suggest that the proportion of patients found to have nodal metastasis increases significantly, with strong trends towards significant upward aggregate stage migration (49). Unfortunately, these studies do not yet provide data on the survival impact of these quality improvement measures (50-52). Despite the paucity of data on survival impact and cost-effectiveness of these corrective interventions, it seems prudent to narrow or eliminate the quality gap in pathologic nodal staging, given its well-documented adverse impact on patient survival.

It is also important to emphasize that the results of Z0030 should be applied to patients with relatively early clinical stage NSCLC. These results cannot automatically be extrapolated to patients with more advanced disease. In addition, we propose that systematic sampling must be performed at least as rigorously as in Z0030 in order to

provide sufficient quality pathologic staging for patients who undergo staging by that strategy. Calling a procedure 'systematic sampling' or 'mediastinal lymph node dissection' does not necessarily make it so. The definitions must be based on the actual lymph nodes retrieved from specific stations, all of which must be clearly labeled for, and examined by, the pathologist.

In conclusion, there is a great need to heighten general awareness of the prevalence and severity of the quality gap between optimal, recommended, nodal staging of resectable lung cancer, and actual practice. This awareness campaign must be sponsored and supported by all the clinical professional groups with influence over the problem, including associations of surgeons, pathologists, medical oncologists and radiation oncologists, and their various guidelines-making bodies. Research into the evaluation and implementation of corrective solutions must be supported by funding agencies, in order to provide clear evidence with which healthcare policymakers can develop incentives that will ultimately facilitate the elimination of this major quality of care deficit.

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None.

Footnote

Conflicts of Interest: Dr. Osarogiagbon has filed a patent application for a surgical lymph node specimen collection kit; Dr. Darling has declared no conflict of interest.

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Diagnostic and therapeutic value of computed tomography guided coil placement after digital subtraction angiography guided video-assisted thoracoscopic surgery resection for solitary pulmonary nodules

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Background: With the widespread use of general health examinations, the detection rate of pulmonary nodules has increased; however, locating the pulmonary nodules is still a challenge.

Methods: We reviewed cases that underwent computed tomography (CT)-guided coil localization followed by real-time digital subtraction angiography (DSA)-guided accurate resection of solitary pulmonary nodules (SPNs) using video-assisted thoracoscopic surgery (VATS) at our hospital, and we evaluated the clinical value. From September 2011 to October 2014, 116 cases with SPNs were treated in our unit. The lesion was preoperatively localized using coil placement under CT guidance, and the patients were subsequently transferred to the hybrid operating room. VATS wedge resection with real-time DSA guidance was performed, and further processing was conducted in accordance with the intraoperative pathological diagnosis for these lesions.

Results: Coil localization, which averaged 15.30±3.20 min, was successful in all patients (100%), while VATS wedge resection took 24.20±12.10 min and lobectomy or segmentectomy took 88.8±36 min. The pathological results revealed malignant lesions in 61 cases and benign lesions in 55 cases.

Conclusions: Preoperative CT-guided coil localization for SPNs had a high accuracy with no serious complications. Following real-time DSA-guided VATS resection, the lesions could be accurately removed with a cutting edge distance of >2 cm to the lesion, which may help diagnose and treat the SPN simultaneously.

Keywords: Lung; lung cancer; thoracoscopy/video-assisted thoracoscopic surgery (VATS); surgery; complications

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Introduction

The accepted definition for solitary pulmonary nodule (SPN) is a single periphery defined well and visible on a computed tomography (CT) scan, a lesion of ≤30 mm in diameter that is completely surrounded by pulmonary parenchyma, and a lesion without pulmonary atelectasis, pulmonary hilar enlargement, or pleural effusions (1,2). With the popularization of CT examination and low-dose CT screening, SPNs can be discovered easily. When the malignant probability is >60%, video-assisted thoracoscopic surgery (VATS) is a recommended processing strategy for diagnosis and radical treatment (3) to obtain an integrated diagnosis and treatment. However, the intraoperative quick finding and accurate positioning of SPNs that are >2 cm deep with a nodule <8 mm in diameter is difficult. Most intrapulmonary focal ground-glass opacities (fGGOs) increase the difficulty because they are soft, and some surgeons have even converted to thoracotomy, which is not minimally invasive (4).

From September 2011 to October 2014, we assessed 116 patients according to the diagnosis and treatment of the clinical pathway (5). We localized the SPNs by using CT-guided coil placement followed by resection of the SPNs by VATS in combination with digital subtraction angiography (DSA) in a hybrid operating room. We report on this method of quick localization and accurate resection, which achieved satisfactory results.

Technology

Equipment

The following equipment was used to conduct our study: a double spiral CT (Siemens Medical Solution, Forchheim, Germany), FD20 DSA (Philips Healthcare, Best, the Netherlands),Tornado Embolization Coil (MWCE-35-3-4, diameter: 4 mm; Cook Inc., Bloomington, IN, USA), percutaneous transhepatic cholangiography needle (18 G × 150 mm); and high-definition endoscopic camera system (Echelon Flex 60; Johnson & Johnson, New Brunswick, NJ, USA).

Surgical procedure

Preoperative localization

In the following description of the surgical procedure, we have selected one patient as an example. A 64-year-old man was admitted for a shadow in the right upper lobe. The CT scan showed a ground-glass opacity located in the right upper lobe (diameter, 1.3 cm; the distance to the pleura, 2.1 cm). Early in the operating day, the patient was sent to the CT room, and the supine position was selected as the shortest distance to perform a needle biopsy. The superficial needling point was localized using a ruler in combination with three-dimensional reconstruction, and careful attention was paid to avoid structures such as the heart, trachea, blood vessels in the mediastinum and lungs, ribs, scapula, and liver. The best pathway for measuring the depth and angle of needle insertion was chosen. After local disinfection and anesthesia, we inserted the needle according to the depth and angle previously measured, and placement of the needlepoint was adjusted again using a CT scan. The stylet was removed, and a Cook vascular embolization coil was inserted to localize the nodule (*Figure 1*). The needle was removed, and another CT scan was performed to ensure that the coil was in the right place and that no complications (e.g., hemothorax or pneumothorax) had occurred. The CT image was sent to the hybrid operation room for VATS operation.

Anesthesia administration and the surgical incision

The patient was ventilated with a double-lumen endotracheal tube while under general anesthesia, and he was placed in the lateral decubitus position (on the side that had a collapsed lung) (*Figure 2*). The surgeon was on the patient's ventral side.

A 1-mm incision was made in the seventh intercostal space at the site of the midaxillary line, which was used for thoracoscope insertion. The second incision was made depending on where the lesion was located. For example, if in the upper lobes, a 1.5 cm port was created in the line of the anterior axillary; if in middle and lower lobes, then the port was created at the site of the fourth intercostal space. A 1.5 cm utility port was placed in the ninth intercostal space at the posterior axillary line as auxiliary ports. This port was extended when we removed the specimen during the lobectomy.

Real-time DSA-guided VATS excision

To ensure coil localization with DSA, we adjusted the C-shaped arm and grasped the surrounding lung tissues accurately using sponge forceps with discontinuous and multi-angle real-time fluoroscopic guidance in order to confirm the scope of the operation (*Figure 3*). Wedge resection was performed using a stapler (Echelon Flex 60) about 2-3 cm around the lesion (*Figure 4*). The specimen was withdrawn in an endoscopic retrieval bag. The coil was

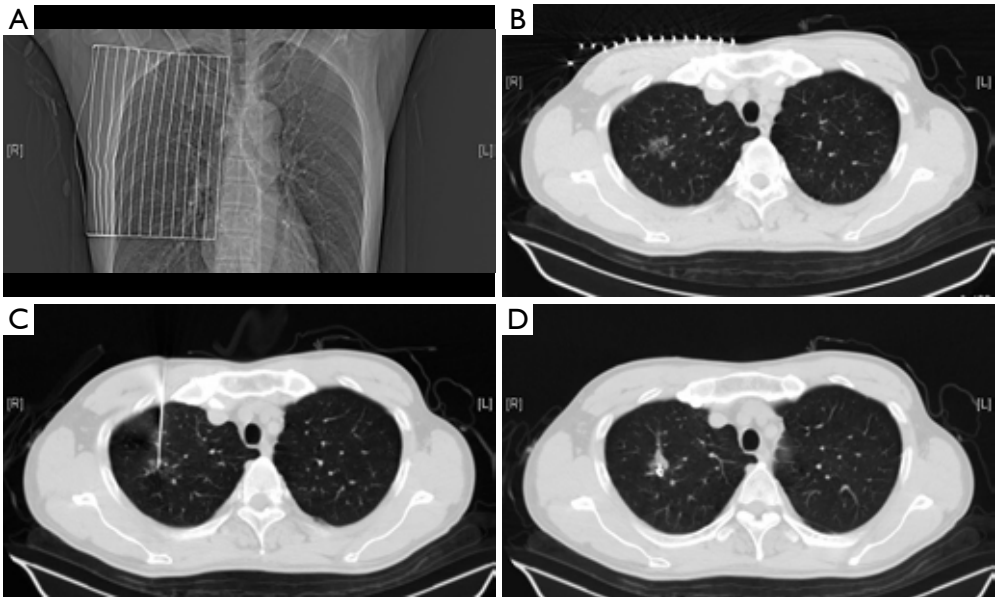

Figure 1 (A) The ruler is placed on the surface of the chest wall; (B) the depth and angle of the needle insertion is measured according to the location of focal ground-glass opacities (fGGOs) guided by computed tomography (CT); (C) the needle is inserted along the optimal path closest to the lesion; (D) the stylet is removed, the coil is placed, and the patient is assessed for any serious complications.

Figure 2 The hybrid operating room and the patient's position.

visualized again using fluoroscopy, which was followed by an immediate frozen-section histopathologic examination. If benign, the bleeding was stopped, and a small chest tube was placed without any further resection. If malignant, a lobectomy followed by lymph node dissection was performed, and the specimen was sent for routine histologic examination.

Clinical experience

After excluding patients with multiple pulmonary nodules or confirmed malignant or metastatic tumors, 116 SPN cases were treated in our unit from September 2011 to October 2014. Among them, 49 were men and 67 were women with a mean age of 55.2±23.5 years, and the mean diameter of the lesions was 12.2±5.12 mm (*Table 1*). Sixty-one cases had pure ground glass opacity, 21 had a high-density nodule, and 34 had a mixed density ground glass opacity; the distance to the visceral pleura was (15.13±12.54 mm). The distribution of the lesions was as follows: 31 in the left upper lung, 22 in the left lower lung, 40 in the right upper lung, 4 in the right middle lung, and 19 in the right lower lung. All the medical procedures were approved by the Jinling Hospital's ethics committee.

SPNs in all 116 cases were successfully localized, and the mean duration for location was 15.3±3.2 min. There were 11 (9.48%) and 8 (6.89%) patients who developed asymptomatic pneumothorax and hemorrhage, respectively. Among them, three had pneumothorax and hemorrhage; however, none required a chest tube placement.

The time interval between puncture and surgery was 67.5±48.10 min. Wedge resection was successful in 100% of all the SPN cases. The operative time (from skin incision until the completion of wedge resection) was 24.20±12.10 min. Four patients had a prolonged operative time due to pleural adhesions. There were no conversions to thoracotomy, and no accidental injuries occurred.

The results of the frozen-section intraoperative and routine pathological postoperative examinations were

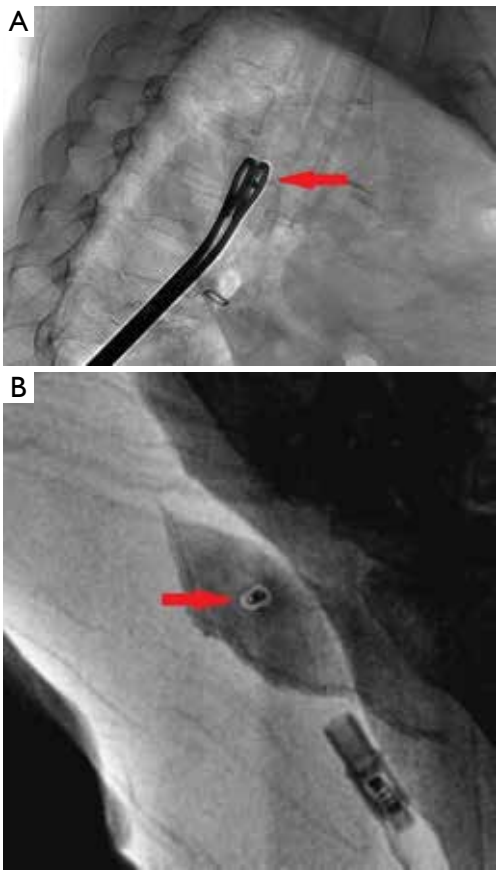

Figure 3 (A) Real-time digital subtraction angiography (DSA) is used to ensure the placement of the coil (red arrow) and to accurately grasp the surrounding lung tissues; (B) the coil is visualized in the specimen, and the range is >2 cm from the incisional margin to the solitary pulmonary nodules (SPNs).

matched in all the cases. The postoperative pathological results are displayed in *Table 2*. The SPNs were malignant in 61 patients, and 49 of which underwent complete lobectomies and lymph node dissection with VATS. The pathological diagnoses on the lymph nodes postoperatively were negative. Twelve patients had adenocarcinoma in situ and underwent wedge resection, and segmentectomies with lymph node dissection or sampling were performed.

The length of stay was 5.1±3.8 days. There were no severe postoperative complications, and no perioperative deaths occurred. We followed 108 (95.12%) patients, with a mean follow-up duration of 7.2±10.5 months. No recurrence or distant metastases were detected in the 61 patients with malignant tumors.

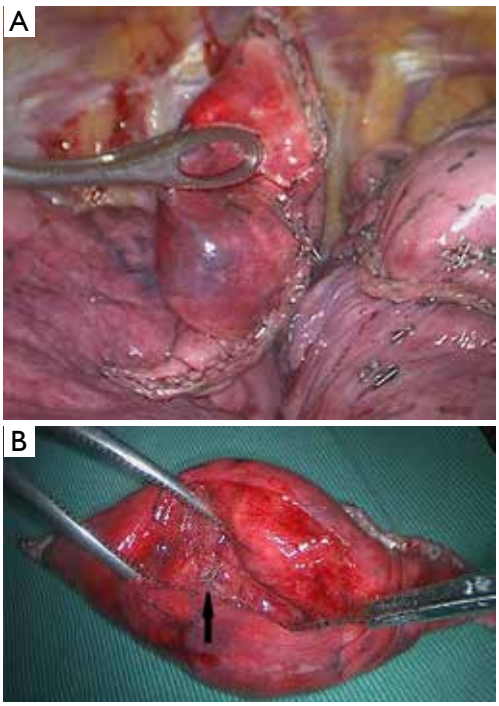

Figure 4 (A) Wedge resection is performed using Echelon Flex 60 staplers; (B) dissection is used to identify the coil and then the lesion is located (black arrow).

Comments

Lung cancer is the number one cause of mortality worldwide; overall, the survival rate is only 15% within 5 years. The survival rate of early stage lung cancer (especially Ia stage lung cancer) can be >80% postoperatively (6). It is difficult to determine the difference between benign and malignant tumors that are <2 cm on CT scans. They may be a malignant tumor such as adenocarcinoma in situ, minimally invasive adenocarcinoma (MIA), invasive adenocarcinoma, or invasive mucous adenocarcinoma. Alternatively, they may be precancerous lesions for atypical adenomatous hyperplasia. Benign lesions include hamartoma, focal interstitial fibrosis, organized pneumonia, inflammation, hemorrhage, etc. If patients with AIS or MIA undergo radical surgery, the 5-year disease-free survival rate may be close to 100%. Therefore, making a definite diagnosis and effective treatment as soon as possible is a clinical dilemma. Clinical treatment urgently requires a method for integrating diagnosis and treatment.

With the rapid development of imaging technology and equipment, especially the popularity of multi detector CT, there are increasing detected rates of SPNs. However,

Table 1 Patients' clinical data

Characteristics	N=116
Age (years)	55.20±23.50
Sex (male/female)	52/64
Lesion location	
Left upper lobe	31
Left lower lobe	22
Right upper lobe	40
Right middle lobe	4
Right lower lobe	19
Diameter (mm)	12.20±5.12
Distance to the pleura (mm)	15.13±12.54
GGO/high density nodules	61/21
Time (from locating the nodule to the beginning of the operation, min)	67.50±48.10
Operation time 1 (from skin incision to completion of wedge resection, min)	24.20±12.10
Operation time 2 (VATS lobectomy and lymph node dissection, min)	88.80±36.00
Volume of chest drainage 1 day postoperatively (mL)	245.00±165.60
Hospital stay (days)	5.10±3.80
Complications after locating the nodules	
Pneumothorax (no. of cases)	11
Hemorrhage (no. of cases)	8

VATS, Video-Assisted Thoracoscopic Surgery.

Table 2 Distribution of the pathological findings in the 116 patients

Pathological results	No. of cases
Primary lung adenocarcinoma	49
Atypical adenomatous hyperplasia	7
Inflammatory lesions	15
Adenocarcinoma *in situ*	12
Pulmonary cyst	8
Sclerosing hemangioma	5
Smooth muscle lipoma	3
Hamartoma	13
Fibrosis nodules with carbon foam deposition	4

qualitative diagnosis still poses to be a problem. Statistically, >40% of SPNs <2 cm in diameter are malignant. Thus, >28% of lung mini nodule (<1 cm in diameter) may also be malignant (7). In this study, 52.58% of the resected lesions were malignant. If SPNs do not receive effective treatment in a timely manner, the malignant lesions could spread or become metastasized. Percutaneous pulmonary aspiration biopsy guided by CT has been widely used in the clinical setting. However, for SPNs <1 cm in diameter, a needle biopsy is still problematic, because the malignant tumor can metastasize along the needle path and the positive rate is low. Therefore, surgery is still required.

Within the past few years, VATS has developed rapidly, and its advantages are reduced pain, minimal trauma, quick recovery, and higher safety. Now an increasing number of surgeons and patients prefer minimally invasive operations for resecting SPNs in the early stage. However, the precise localization of SPNs, especially solid nodules, has always been problematic. Lesions may be approximately localized by reviewing CT scans and three-dimensional reconstruction and by palpating with instruments during surgery. However, if the SPN is <1 cm in diameter and far from the visceral pleura or even GGO, locating it may be difficult. Sometimes surgeons have to extend the resection. Consequently, this extension not only eliminates the advantages of minimally invasive surgery, but it also increases the risk of misjudgment. As a result, it is increasingly important to find an effective way to precisely localize the SPNs preoperatively. Native and foreign surgeons often use CT-guided intralesional

injection of methylene blue, HOOK-wire placement, or intraoperative ultrasonic location; yet, localization may not be precise enough and the location marker may shift during operation (8). Methylene blue injection preoperation works well for SPNs close to the pleura, but if the distance between the nodules and visceral pleura is >1.5 cm, locating the SPN with this method is difficult. Methylene blue may diffuse because of the patients' breathing movement; thus, it is difficult to identify the specific location of the lesion. This situation also occurred when the patients were old or smoked a lot, because the color of their lung surface was too dark to identify any lesions (9). The HOOK-wire location is simple, effective, and quick. HOOK-wire can also lift the lesion to a superficial location. However, sometimes the lesion is so close to the pleura for the wire to hook onto (10), so the methylene blue has to be used in combination (9), which wastes a lot of time. If the nodule is >2 cm in depth or >1 cm in diameter and is located previously using the HOOK-wire method, lobectomy with VATS would still face the problems of a positive surgical margin with too much tissue being removed, making it difficult to guarantee the distance between the nodule and incisional margin. Sometimes the wire is cut off and remains in the body (11,12). Intraoperative ultrasonic location is a useful for the non-invasive detection of nodules that cannot be palpated. However, the operation is complex and highly depends on the operator, and if the nodule is of low density, especially with GGO, this method is useless (13).

SPNs can be resected precisely because of coil placement guided by preoperative CT in combination with intraoperative real-time DSA. The advantages of the COOK coil are as follows. First, the coil is a spiral steel wire coated with fibers; therefore, dislodgement because of respiratory movement or surgical procedure can be avoided. All the cases were successfully localized in this study. Second, the metal material can be easily discovered before and detected after surgery with DSA, so the resection range can be ensured. Third, the nodule adjacent to the coil can be easily found by pathologists using palpation. All lesions <1 cm in diameter were found; thus, the accuracy of the pathological diagnosis can be ensured.

SPN localization performed preoperatively was followed by VATS guided by real-time DSA in the hybrid operation room. A drainage chest tube also prevented complications such as pneumothorax and hemothorax caused by needle biopsy. In the example patient, the involved lung collapsed during surgery. According to the CT image, the puncture site was observed directly on the visceral pleural surface, so the surgeon could grasp the approximate location. Adjustment was performed guided by multi-angle real-time fluoroscopic DSA. Before the incision was closed, the stapler was placed >2 cm away from the SPN. Removal of the specimen and DSA again detected that the coil was visualized, and there was >2 cm from the incisional margin to the SPN. Neither positive surgical margin nor operation error occurred. We achieved a precise excision. This method also provides a new minimally invasive treatment method for patients with poor lung function. This method maximized the remaining lung tissue with a safety distance between the incisional margin and lesion to decrease the incidence of complications. Echelon Flex 60 staplers were used in this study because of their adjustable angle. In our experience, keeping the stapler closed for about 15 s may reduce bleeding and avoid some complications.

We discussed the development status and advancement of CT-guided coil location combined with real-time DSA guided SPN VATS resection. The limitation was obvious, including the single center study design and insufficiencies of the cases. Currently, real-time DSA guided VATS resection of SPN using CT-guided coil placement showed greater advantages than other location methods before operation. This method makes for a precise, effective, and minimally invasive resection of SPN, achieving an integrated diagnosis and treatment that is worth popularizing. Interdisciplinary cooperation will also be an inevitable development direction in the future medicine.

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Footnote

Conflicts of Interest: No funds were used to perform the evaluation. The tested technology was not purchased, borrowed or donated to the study. All authors stated that they had full control of the design of the study, methods used, outcome parameters and results, analysis of data and production of the written report.

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Clinical outcomes of CyberKnife stereotactic radiosurgery for elderly patients with presumed primary stage I lung cancer

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Background: In certain situations, especially in the elderly patient population, a tissue diagnosis of a suspected pulmonary neoplasm is not feasible. Often, a definitive treatment such as stereotactic body radiosurgery is recommended, rather than active surveillance. The aim of this study is to evaluate the efficacy and tolerability of stereotactic body radiotherapy (SBRT) for elderly patients with presumed primary stage I lung cancer without pathological tissue confirmation.

Methods: We performed a retrospective analysis of 25 elderly patients (≥75 years) with presumed primary stage I lung cancer treated with SBRT from 2009–2015. The primary end point was local control (LC); secondary end points were survival and toxicity.

Results: The median follow-up (FU) was 36.0 months (range, 4 to 84 months). The 1-year LC rate was 100%, 3-year LC rate was 78.8%, and 5-year LC rate was 65.7%. The median progression-free survival (PFS) time was 48.0 months (95% CI: 31.2–64.8). The 1-, 3-, and 5-year overall survival (OS) rates were 96.0%, 70.2%, and 50.7%, respectively. The 1-, 3-, and 5-year cancer-specific survival (CSS) rates were 100%, 81.3%, and 67.0%, respectively. No grade 4 or higher toxicity was encountered.

Conclusions: SBRT is safe and effective treatment for patients with presumed primary stage I lung cancer where obtaining pathological confirmation of malignancy is challenging.

Keywords: Clinical diagnosis; stage I lung cancer; stereotactic body radiotherapy (SBRT); stereotactic ablative radiotherapy (SABR); elderly

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Introduction

The solitary pulmonary nodule (SPN) is defined as a radiographic opacity up to 30 millimeters in diameter with at least two-thirds of its margins surrounded by lung parenchyma (1). SPNs are being increasingly detected in recent years due to the more widespread use of imaging and screening chest computed tomography (CT) scans. Surgical resection is primary treatment for a pathological diagnosis of early stage non-small cell lung cancer (NSCLC) in a medically fit patient who can withstand the stress of surgery. Stereotactic body radiotherapy (SBRT), also called stereotactic ablative radiotherapy (SABR), has had excellent success in the treatment of stage I NSCLC in medically inoperable patients, and it has been reported

to have comparable local control (LC) to surgery with minimal morbidity. Multiple studies have documented that SBRT achieves a very high LC and can improve survival in medically inoperable patients with early lung cancer (2,3) who are often frail and have competing risk factors for death.

For operable patients, the equipoise to justify randomization to SBRT compared to surgery in clinical trial is clearly more difficult, and thus several studies have been terminated due to lack of enrollment (4). Recently, a pooled analysis of two randomized trials (STARS and ROSEL) was performed to assess SBRT versus surgery for operable stage I NSCLC. Notably, they found that SBRT was associated with a higher 3-year overall survival (OS) than surgery (95% *vs.* 79%, P=0.037) (5). This suggests that in certain patients, SBRT may achieve outcomes comparable to surgery.

A large number of lung nodules are detected due to the widespread use of chest CT scans. However, without a tissue biopsy, radiographic features alone cannot confirm the absolute presence of a malignancy. Not all lesions are amenable to endobronchial biopsy, and image-guided biopsy can fail to diagnose smaller lung lesions (≤20 mm). Given the poor functional status, comorbidities, and concerns about toxicity, including pneumothorax, infection, and bleeding many patients, especially elderly patients, refuse or do not undergo a biopsy due to concern of toxicities. When patients refuse biopsy or surgical resection, an alternative of active surveillance may be suggested. However, for NSCLC, even at early stage, the lack of treatment is often fatal (6). A recent meta-analysis assessing seven cohort studies (4,418 patients) and 15 randomized controlled trials (1,031 patients) evaluated mortality without treatment in NSCLC patients. The pooled mean survival for patients without anticancer treatment was 7.15 months (5,6). Even for T1 early stage NSCLC, the median survival among a cohort of 1,432 patients who did not undergo surgical resection or treatment with chemotherapy or radiation was only 13 months (7). Thus, definitive treatment is usually recommended, rather than surveillance. In addition, definitive treatment generally should be performed without delay because waiting times >4 weeks can cause tumor growth (8) and new nodal and distant metastases even for early-stage NSCLC (9). Several groups have reported their findings on SBRT in patients with SPNs clinically diagnosed as lung cancer who lack tissue confirmation (10-12). The 3-year LC values range from 80% to 94%, which are comparable to outcomes of SBRT for pathological diagnosed early NSCLC patients (11,12).

In this study, we performed a retrospective analysis of elderly patients with clinically diagnosed primary stage I lung cancer lacking tissue diagnosis who were treated with SBRT at our institution, and we assessed LC (in-field), survival, and toxicity.

Methods

Patients

We performed a retrospective analysis of patients with presumed primary stage I lung cancer patients underwent SBRT (CyberKnife®, Accuray, Sunnyvale, CA, USA) at our institution from March 2009 to March 2016. Prior to treatment, all patients underwent comprehensive staging, including head magnetic resonance imaging and 18fluorine-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT), tumor markers, routine blood tests, and blood chemistry panels. The inclusion criteria were presumed primary stage I lung cancer without tissue confirmation; age ≥75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2. Patients who had a history of cancer or were diagnosed pathologically or suspected as having small cell lung cancer (SCLC) due to the elevated of neuron specific enolase, were excluded from this study. The patients' conditions were comprehensively assessed by radiologists and oncologists. The study was approved by the Institutional Ethical committee Written informed consent was obtained from the patients.

Treatment

SBRT was performed (CyberKnife®, Accuray, Sunnyvale, CA, USA) using technology which was previously described by our group (13). A total of nine patients who were ineligible for the "X sight lung" option were thus implanted with one to three gold fiducials inside or near the tumor to define the tumor position and to use for tumor tracking during SBRT. Approximately 1 week after fiducial placement, CT simulation was performed for treatment planning (BrillianceTM Big Bore, Philips, Netherlands). Gross tumor volume (GTV) was defined as the tumor volume delineated on lung windows settings. The planning target volume (PTV) was obtained by expanding the GTV by 3 mm uniformly in all directions. The dose was prescribed based on the isodose line and covered the PTV. SBRT was delivered to a total dose of 40 to 60 Gy over

2 to 5 days. The dose equivalence was used as a linear quadratic model and considered by assuming α/β=10 Gy for the tumor. The biological effective dose (BED) ranged from 83–150 Gy, and the median BED was 132 Gy. Dose and fractionation schedules were developed based on the patient's performance status, tumor size, and location.

Follow-up (FU) and statistics

The endpoints of this study were LC, cause-specific survival, OS and treatment toxicity. All patients underwent clinical examination and CT scan for evaluation of treatment results 4–6 weeks after SBRT, then every 3 months for the first 2 years, and then the every 6–8 months until death.

Acute and late toxicity was assessed according to the RTOG and RTOG/EORTC toxicity scales. Responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) (14). Local failure was defined as growth following initial tumor shrinkage or progression on two consecutive scans, with the date of local failure backdated to the earliest scan showing progression. Regional recurrences were defined as hilar, mediastinal, or supraclavicular nodal enlargement on CT. Distant failures were defined as any failure outside of the thorax, as well as malignant pleural or pericardial effusions and disease in different lobes. The OS was assessed from the start of SBRT until death, censoring the last FU date. The cancer-specific survival (CSS) was assessed from the start of SBRT until cancer progression death, censoring the last FU date. The progression-free survival (PFS) was calculated from that same time until disease progression. The OS and CSS curves were estimated by Kaplan-Meier analysis and were compared using the log-rank test and the Cox model. The influence of variables on survival was investigated using univariate analysis (Cox model). Statistical analysis was performed with commercial software, (SPSS® version 21.0, SPSS Inc., Chicago IL, USA), and $P<0.05$ was considered statistically significant for all analyses.

Results

Patient and tumor characteristics

From March 2009 to March 2016, 25 patients with a median age of 78 years from our CyberKnife center were enrolled in the study. The patient characteristics are detailed in *Table 1*. The median FU was 36.0 months (range, 4 to 84 months). The most common tumor localization was the upper lobe [17 of 25 patients (68%)]. The main cause of inoperability and lack of tissue confirmation of lung cancer was the presence of comorbidity [19 of 25 patients (76%)]. Six patients (10.5%) refused biopsy due to concerns of toxicity. Twenty-three patients (92%) were ineligible for surgery on account of their advanced age and/or comorbidities. Two patients (8%) refused primary surgery.

LC

Local progression occurred in four patients (16%), regional recurrence in two patients (8%) and distant metastasis in six patients (24%). Among patients (n=8) with tumor sizes ≤20 mm, no local progression occurred. Overall, the 1-year actuarial LC rate was 100%, 3-year actuarial LC rate was 78.8%, and 5-year actuarial LC rate was 65.7%. Actuarial LC of the SPNs is shown in *Figure 1*. In univariate analysis, pre-treatment aximum standardized uptake value (SUVmax) (<5 *vs.* ≥5), age (< 80 *vs.* ≥80), BED (120 *vs.* ≤120 Gy), and stage (T1a *vs.* T1b) were not significantly related to LC (*Table 2*).

Survival

Median FU for all patients was 36.0 months. At the time of analysis, 5 of the 25 patients (20%) died of disease progression and 4 patients died of comorbidities. The 3-year PFS was 66.3% and the 5-year PFS was 17.1%. The median PFS time was 48.0 months (95% CI: 31.2–64.8). The 1-, 3-, and 5-year OS rates were 96%, 70.2%, and 50.7%, respectively. The 1-, 3-, and 5-year CSS rates were 100%, 81.3%, and 67.0%, respectively. The Kaplan-Meier PFS and the CSS and OS curves are shown in *Figures 2,3*, respectively. In univariate analysis, SUVmax (<5 *vs.* ≥5), age (<80 *vs.* ≥80), BED (>120 *vs.* ≤120 Gy) and stage (T1a *vs.* T1b) were not significantly related to PFS, CSS or OS (*Table 2*).

Toxicity

There have been no cases of acute or late grade 4 toxicity or possible treatment-related death. The most common acute toxicity was grades 1–2 fatigue (5/25,20%). Acute grades 1–2 radiation pneumonitis occurred in two patients (8%), and acute grade 3 radiation pneumonitis was observed in two patients (8%), who needed to be treated with steroid inhalers and oral steroids for a short duration of time. Late grade 3 radiation pneumonitis was observed in one patient (4%) at 6 months after SBRT.

Table 1 Patient and tumor characteristics

Characteristic	No. [%]
No. of patients	25
Age, median (range)	78 [75–91]
≤80	15 [60]
>80	10 [40]
Sex	
Male	20 [80]
Female	5 [20]
Reason for lack of biopsy	
Age	6 [24]
Vascular disease	5 [20]
Vascular disease + COPD	3 [12]
More than three comorbidities	3 [12]
COPD	3 [12]
COPD + age	2 [8]
Vascular disease + age	2 [8]
Metabolic alterations	1 [4]
Performance status	
1	20 [80]
2	5 [20]
T stage	
T1a	8 [32]
T1b	17 [68]
Lesion volume median (cc)	
Median (range)	16.0 (4.2–23.1)
≤10.0 mL	3 [12]
>10 mL	22 [88]
BED (Gy)	
Median (range)	136 (83.0–150.0)
≤120 Gy	10 [40]
>120 Gy	15 [60]
Tumor location	
Right upper lobe	9 [36]
Middle lobe	1 [4]
Right lower lobe	1 [4]
Left upper lobe	8 [32]
Left lower lobe	6 [24]
FDG-PET/CT	
SUVmax median (range)	5.5 (3.1–13.2)
≤5.0	10 [40]
>5.0	15 [60]

BED, Biological Offective Dose; COPD, Chronic Obstructive Pulmonary Disease; FDG-PET/CT, ^{18}fluorine-fluorodeoxyglucose-positron emission tomography/computed tomography.

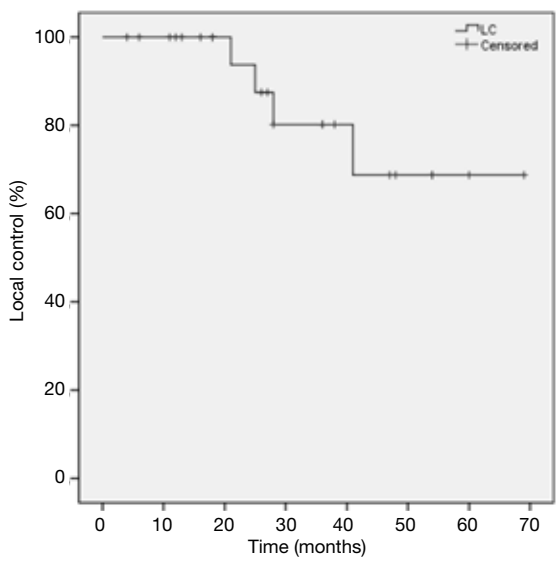

Figure 1 Kaplan-Meier actuarial local control (LC).

Discussion

SBRT is an accepted standard therapy for stage I NSCLC in patients deemed medically unfit for or refusing surgery. Multiple studies have confirmed that SBRT is safe and effective for a clinically diagnosed primary stage I lung cancer (10-12). In this study, we addressed the question of whether SBRT may achieve good LC, survival, and toxicity profile in an even more frail elderly patient population who refused or cannot undergo biopsy of their presumed early stage NSCLC. We demonstrate that SBRT for elderly patients with presumed primary stage I lung cancer who lack tissue confirmation achieved good LC and CSS with minimal toxicity.

Table 2 Univariate analysis for LC, PFS, CSS, OS

Variables	LC		PFS		CSS		OS	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
SUVmax (≤5.0 *vs*. >5.0)	0.468 (0.047–4.694)	0.519	0.316 (0.065–1.547)	0.155	0.024 (0.000–47.240)	0.334	0.022 (0.000–6.007)	0.183
T (T1a *vs*. T1b)	24.668 (0.000–12,701,550.12)	0.633	1.246 (0.150–10.385)	0.839	26.211 (0.001–1,026,987.058)	0.545	0.871 (0.177–4.279)	0.865
BED (>120 *vs*. ≤120 Gy)	1.095 (0.108–11.110)	0.939	0.705 (0.165–3.013)	0.637	30.753 (0.004–230,288.575)	0.452	1.429 (0.292–7.002)	0.660
Age (≤80 *vs*. >80 years)	0.934 (0.097–8.986)	0.953	1.190 (0.230–6.165)	0.836	0.620 (0.069–5.563)	0.669	1.240 (0.307–4.998)	0.763

LC, local control; PFS, progression-free survival; CSS, cancer-specific survival; OS, overall survival; SUVmax, maximum standardized uptake value; BED, biological effective dose.

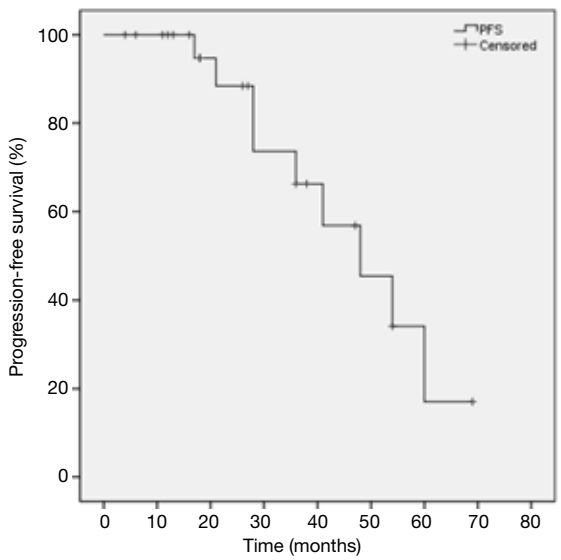

Figure 2 Kaplan-Meier curves of progression-free survival (PFS).

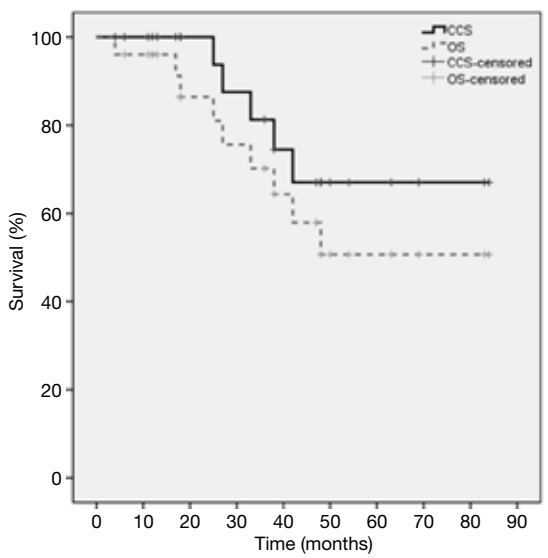

Figure 3 Kaplan-Meier curves of cancer-specific survival (CSS) and overall survival (OS).

Pathologic diagnosis is the most accurate diagnosis for lung tumors. However, there is an inherent false-negative rates for biopsy, in addition to unique risks and potential morbidities associated with both CT-guided and EBUS-directed lung biopsies (15). Therefore, it is necessary to improve the sensitivity and specificity of the procedures and to increase the rate of accurate diagnosis, as well as to minimize procedure-associated morbidities such as pneumothorax, bleeding, and infection. Chest CT is one of the most reliable modalities for identifying pulmonary malignancies, and given advances in the improved resolution of CT scans with thin slice thickness, high resolution, and contrast enhancement, serial images showing growth of a lung nodule in this patient population may supplant a tissue diagnosis in certain cases. High resolution CT can evaluate the detailed characteristics of lung nodules, such as their size, morphology, and type of opacity. FDG-PET/CT scanning is also increasingly used to differentiate pulmonary malignancies from benign nodules by means of having higher glucose metabolism. American College of Chest Physicians (ACCP) review calculated the sensitivity and specificity of FDG-PET/CT scanning to be 94.2%

Table 3 Efficacy of SBRT in patients with clinically diagnosed primary lung cancer

Study	N	Median age (year)	Median diameter (mm)	Dose (Gy)	Median FU (mo)	3-year OS (%)	5-year OS (%)	3-year LC (%)
Inoue (10) [2009]	58	77	≤20	30–70 Gy/2–10 f	–	89.8	89.8	–
	57		>20		–	60.7	53.1	–
Verstegen (11) [2011]	382	74	Mean 28.4	60 Gy/3–8 f	29.5	55.4	–	91.2
Takeda (12) [2012]	58	79	26.5 [10–53]	40–50 Gy/5 f	20.2	54.0	–	80.0
Sakanaka (22) [2014]	37	77	20 [7–42]	48 Gy/4 f	39	74.2	–	94.0
Yoshitake (23) [2015]	88	76	19 [8–40]	48 Gy/4 f	23	80.0	–	90.0
Fujii (24) [2015]	54	76	19 [8–45]	mBED 110 Gy	41	90.0	–	94.0
Current study	25	78	25 [17–30]	40–60Gy/2–5 f	36	70.2	50.7	78.8

SBRT, stereotactic body radiotherapy; FU, follow-up; OS, overall survival; LC, local control; mBED, the median biological effective dose.

and 83.3%, respectively, for the identification of malignant pulmonary nodules (16). Several quantitative prediction models using clinical and radiological criteria have been developed to assist clinicians in discriminating malignant from benign nodules (17-20). Three models incorporate clinical and CT nodule characteristics, such as age, smoking, history of cancer, nodular diameter, location and morphology (17), and a fourth model (Herder *et al.*) added FDG-PET/CT to the Mayo Clinic model. Recently, a study to compare the performance of these models in a population of patients recruited from a UK teaching hospital showed that the highest accuracy was seen for the model described by Al-Ameri *et al.* incorporating FDG avidity (21) into the model to predict, based on imaging parameters, who had NSCLC. ACCP also recommended that those with a risk greater than 60% of having a pulmonary malignancy should receive further treatment (16).

A number of investigators worldwide have described outcomes after SBRT in patients without a pathological diagnosis (*Table 3*), (10-12,22-24). In those studies, SBRT was reportedly well tolerated, with 3-LC rates between 80% and 94%. The 3-year OS rates were in the range of 54% to 90%. The survival results of the current study are comparable to those of published series despite the generally more advanced age in the current study population. Over the last decade, the use of lung SBRT without biopsy has increased (25). Inoue *et al.* (10) analyzed the outcomes of 115 stage I clinically diagnosed lung cancer patients treated with SBRT. The 3-year and 5-year OS rates for patients with a tumor size ≤20 mm in diameter (n=58) were both 89.8%, and those with tumors >20 mm (n=57) were 60.7% and 53.1% (P<0.0005), respectively. Sakanaka *et al.* reported the results of 37 patients clinically diagnosed with primary stage I lung cancer empirically treated with SBRT. After a median FU of 36 months, the 3-year OS was 89.9% in patients with T1a tumors versus 51.7% in patients with T1b/T2a tumors (22). The researchers suggested that tumor size was a prognostic factor for OS in SBRT for clinically diagnosed primary lung cancer. Of note this is compatible with a previous report of SBRT for pathologically diagnosed NSCLC (26). Verstegen *et al.* reported a comparison between 209 clinically diagnosed patients and 382 pathologically confirmed NSCLC patients who underwent SBRT, and concluded that OS and LC were similar in large groups of patients with or without pathological diagnosis (11), suggesting that risk of overtreatment of truly benign nodules is low if strict radiological and patient characteristics are used to guide treatment decisions for nodules lacking tissue confirmation. Other studies also reported that there was no difference in OS between confirmed NSCLC patients and clinically diagnosed patients (12,27). A recent meta-analysis confirmed an association of high pre-RT SUVmax of primary tumor with poor OS and LC in NSCLC patients receiving RT. Such an association seems to be particularly strong for patients with stage I NSCLC receiving SBRT (28). In the present study, four patients had local recurrences, with the time to recurrence from treatment of 21, 25, 28, and 41 months. All patients with local recurrences had T1b tumors that were among the largest tumor sizes in the present cohort. Despite having a numerically notable effect on outcomes, likely due to the small patient sample size and inadequate

power, tumor size (T1a *vs.* T1b) and SUVmax (<5 *vs.* ≥5) were not significantly related to survival and LC.

Elderly patients and those with poor pulmonary function or multiple comorbidities often are not candidates for biopsy. Therefore, elderly patients with clinically diagnosed lung cancer are now offered SBRT, a minimally invasive definitive therapy for early stage NSCLC. A National Cancer Data Base analysis showed that a significant improvement in survival was noted for elderly patients who receive SBRT relative to observation alone. SBRT should be considered as part of a patient's treatment options for early stage NSCLC, and providers should be aware of this minimally invasive treatment option for elderly patients with early stage NSCLC (29). Mancini *et al.* demonstrated that elderly patients (≥75 years) treated with SBRT for early-stage NSCLC appear to have equivalent OS, LC and toxicity rates as compared to younger patients. For elderly patients, the rate of grade ≥3 pneumonitis was 8.7% (30). In our study, two of the 25 patients (8%) similarly developed grade 3 radiation pneumonitis, and the toxicities seen in the current study are comparable to those of previous trials.

Conclusions

The results of the present study support the efficacy and safety of SBRT in elderly patients with clinically diagnosed primary stage I lung cancer. In cases where tissue diagnosis is possible, histological confirmation of malignancies should be the gold-standard for work-up for a patient with suspected early stage NSCLC. However, patients should be counseled about the pros and cons of empiric SBRT without tissue confirmation in situations where a tissue diagnosis is not technically feasible or biopsy could be associated with an unacceptable risk profile. This research has several limitations, including a limited sample size, and further studies of empiric SBRT are needed to be conducted to appropriate dose levels for elderly patients with a poor performance status lacking tissue confirmation of malignancy.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare

Ethical Statement: The study was approved by the Institutional Ethical Committee (No. 2016NZGKJ-016) and written informed consent was obtained from all patients.

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Sublobar resection for early-stage lung cancer

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Abstract: Since the 1995 report of the prospective randomized trial of lobectomy versus sublobar resection for stage I non-small cell lung cancer (NSCLC) performed by the the Lung Cancer Study Group, lobectomy remains the standard of care for the surgical management of stage I NSCLC. Sublobar resection has been typically used for high-risk patients who are operative candidates but for whom a lobectomy is contraindicated. Recent advances in imaging and staging modalities and improved spatial resolution of computed tomography (CT) scan have refined the presentation and diagnosis of early-stage NSCLC. The detection of small tumors and ground-glass opacity (GGO) appearance associated with a favorable histology have led to the increased use of sublobar resection in many institutes to include good-risk patients. There is an increasing body of evidence that sublobar resection may achieve oncological outcomes similar to those with lobectomy in early-stage NSCLC, especially that 2 cm or less in size. However, whether or not sublobar resection constitutes adequate treatment for small-sized lung cancer or for the radiographic "early" lung cancer such as a GGO-dominant lesion is still being prospectively investigated. Sublobar resection will be expected to play an important role as a primary treatment option for patients with small stage IA NSCLC, based on an anatomical functional advantage over lobectomy as well as comparable prognostic outcomes between sublobar resection and lobectomy.

Keywords: Non-small cell lung cancer (NSCLC); sublobar resection; prognosis; early-stage lung cancer; surgery

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Introduction

In 1995, the Lung Cancer Study Group (LCSG) reported the only randomized trial that compared lobectomy to sublobar resection for the treatment of stage IA non-small cell lung cancer (NSCLC) (1,2). They found an increased risk for locoregional recurrence, a reduced 5-year survival rate, and no statistical evidence for the preservation of pulmonary function, and thereby disproved the speculation that sublobar resection had an outcome that was comparable to that of lobectomy, and reinforced the need for lobectomy in early-stage patients. Thus, sublobar resection was considered to be a "compromise" operation for high-risk patients who were not candidates for lobectomy because of advanced age, severely impaired pulmonary function, or other comorbidity (3-7).

Although lobectomy remains the standard of care for patients with stage IA NSCLC, recent advances in clinical imaging/staging modalities and the increased identification of smaller tumors by computed tomography (CT) screening have led to a resurgence of interest in sublobar resection for these tumors (8-13). Several recent studies have demonstrated comparable recurrence and survival rates for lobectomy and sublobar resection, even in good-risk patients with small stage I lung cancer (14-18). In addition, due to improvements in CT resolution, a ground-glass opacity (GGO) appearance on thin-section CT (TSCT) has been reported to be associated with a favorable histology such as non- or minimally-invasive adenocarcinoma in lung cancer (19-21). These GGO lesions are also likely to be amenable to sublobar resection.

If sublobar resection is equivalent to lobectomy with respect to their oncological results for the surgical treatment of lung cancer, the potential benefits of sublobar resection

include the preservation of vital lung tissue and a chance for a second resection with a subsequent primary tumor. Thus, sublobar resection plays an important role in the surgical treatment of patients with NSCLC who are diagnosed at an early stage.

This article reviews the current status of sublobar resection for early-stage NSCLC, with particular attention to issues such as tumor size, type of sublobar resection (segmentectomy versus wedge resection), surgical margin, radiology-pathology correlation, and pulmonary function.

History

In the early half of the 20th century, pneumonectomy was considered the only appropriate treatment for primary lung cancer. However, due to the unacceptably high mortality rate associated with pneumonectomy at that time, lobectomy evolved as the treatment of choice for resectable lung cancers. As a further extension of the anatomic approach to lung resection, thoracic surgeons began to explore the use of segmentectomy for early-stage lung cancer in high-risk patients (22-26). Subsequently, many studies reported that segmentectomy was useful as a compromise operation in selected, high-risk patients (3,27,28), since Jensik and colleagues first described its use for lung cancer resection in 1973 (22). Several of these studies advocated sublobar resection (wedge resection or segmentectomy) as an appropriate treatment for patients with early-stage lung cancer (3,27).

Due to speculation about the prospect of sublobar resection for early-stage NSCLC, the Lung Cancer Study Group (LCSG) conducted a prospective, randomized trial that compared lobectomy to sublobar resection for the treatment of clinical T1N0 NSCLC, and the results were published in 1995 (1). This trial demonstrated a 3-fold increase in local recurrence and a decrease in overall survival after sublobar resection. Consequently, the need for formal lobectomy in early-stage NSCLC was reinforced. Since this publication, many studies have retrospectively supported these results; i.e., lobectomy offers an overall and disease-free survival advantage (*Table 1*) (1,15,29-43).

However, the 1995 LCSG study (1) received several major criticisms: (I) a high percentage of patients in the sublobar group underwent wedge resection other than anatomic segmentectomy; (II) routine chest CT examination was not required either preoperatively or for postoperative surveillance; (III) the difference in the prognosis between sublobar and lobar resections was relatively small; (IV) the analysis regarding the preservation of postoperative pulmonary function was inadequate between sublobar and lobar resections, and so on (16,44). In addition, recent advances in imaging and staging modalities and the detection of smaller tumors by TSCT scan have rekindled interest in sublobar resection for early-stage NSCLC. Thus, single-institutional retrospective investigations have demonstrated that sublobar resection is equivalent to lobectomy in patients with early-stage NSCLC and especially for smaller tumors (2 cm or less in diameter) (14,15,45,46). Currently, two prospective, randomized, multi-institutional phase III trials are being conducted by the Cancer and Leukemia Group B (CALGB 140503) and the Japan Clinical Oncology Group (JCOG 0802) (47). Additionally, according to the correlation between TSCT findings and the pathology of lung cancer, lung nodules with a GGO appearance on TSCT have been considered to be "early" lung adenocarcinoma (6,48). Whether or not sublobar resection constitutes adequate treatment for small peripheral cancer in general or for tumors in which the preoperative radiographic features suggest an "early" adenocarcinoma is still being investigated.

Tumor size

It is well known that tumor size is a recognized prognostic variable in NSCLC (49). Over the past decade, many studies have demonstrated improved survival and local control for patients with T1N0 tumors of 2 cm or smaller compared with larger tumors (11,30,50), although the LCSG trial (1) showed no survival advantage based on tumor size. Data from the recent lung cancer staging project headed by the International Association for the Study of Lung Cancer (IASLC) also found an improvement in survival for stage IA tumors less than 2 cm in diameter compared with those 2 to 3 cm in size and led to the reclassification of T1 tumors in the revised staging system (51,52). In this revision, tumors that measure 2 cm or less are considered to be T1a and those of 2 to 3 cm are T1b (52). The appropriateness of sublobar resection for small lung tumors, especially those 2 cm or less in size, has recently been addressed by many researchers. *Table 2* summarizes the results of sublobar resection for NSCLC ≤2 cm (14-17,34,36,39,45,53-56). There is a growing body of evidence that sublobar resection may achieve oncological outcomes similar to those with lobectomy in this setting of smaller tumors. Patients with NSCLC of 2 cm or smaller may represent a population in whom sublobar resection should be considered.

Table 1 Survival data in studies that compared sublobar resection to lobectomy for patients with NSCLC

Author [year]	Study design	No. of Patients	Stage	Compromised *vs.* intentional	Type of sublobar resection	Mortality (%)		5-YSR			Local rec. rate		
						Lobectomy	Sublobar resection	Lobectomy (%)	Sublobar resection (%)	P	Lobectomy (%)	Sublobar resection (%)	P
LCSG [1995]	Pros.; phase III	247	IA	Intentional	Wedge: 40; Seg.: 82	1.6	0.8	69	60	0.08	6.4	17	0.079
Koike [2003]	Pros.; non-randomized	233	IA (≤2 cm)	Intentional	Wedge: 14; Seg.: 60	0	0	90.1	89.1	NS	1.3	2.7	NS
Campione [2004]	Retro.	120	IA	Compromised	Seg.: 21	3	9.5	65	62	NS	2	19	–
Keenan [2004]	Retro.	201	I	Compromised	Seg.: 54	4.8	5.6	67 (4-YSR)	62 (4-YSR)	NS	7.5	11.1	NS
Martin-Ucar [2005]	Retro.; propensity matched study	34	I	N/R	Seg.: 17	5.8	5.8	64	70	NS	2	0	NS
El-Sherif [2006]	Retro.	784	I	Compromised	Wedge: 122; Seg.: 85	–	–	54	40	0.0038	4.2	7.2	0.0204
Chang [2007]	Retro.; SEER database	10,761	IA	N/R	Sublobar: 2,234	–	–	61.4	44.0	<0.0001	–	–	–
Iwasaki [2007]	Retro.	86	<2 cm	Mixed	Seg.: 31	0	0	73	70	NS	3.6	3.2	NS
Kraev [2007]	Retro.	289	I	Compromised	Wedge: 74	–	–	5.8 years (MST)	4.1 years (MST)	NS	–	–	–
Sienel [2007]	Retro.	199	IA	Compromised	Seg.: 49	–	–	83	67	0.01	5	16	0.005
Kilic [2009]	Retro.	184 (age >75)	I	Compromised	Seg.: 78	4.7	1.3	47	46	NS	4	6	NS
Billmeier [2011]	Retro.	679	I-II	Mixed	Wedge: 120; Seg.: 35	1.9	7.1	57	49	NS	–	–	–
Wolf [2011]	Retro.	238	≤2 cm	Compromised	Wedge: 130; Seg.: 24	4	0.	80	59	0.0027	8	16	NS
Varlotto [2013]	Retro.	411	I	Compromised	Wedge: 79; Seg.: 14	–	–	64.5	54.5	NS	24.6	39.5	NS
Altorki [2014]	Retro.	347	IA	Compromised	Wedge: 37; Seg.: 16	1	0	86	85	NS	–	–	–
Okada [2014]	Retro.	634	IA	Mixed	Seg.: 155		0	94.1 (3-YSR)	95.7 (3-YSR)	NS	3.5	1.9	–
Tsutani [2014]	Retro.	239	IA (>50% GGO)	N/R	Wedge: 93; Seg.: 56	0	0	97.6	Wedge: 98.7; Seg.: 98.2	NS	0	0	–

NSCLC, non-small cell lung cancer; 5-YSR, 5-year survival rate; LCSG, Lung Cancer Study Group; Pros., prospective study; Seg., segmentectomy; Retro., retrospective study; NS, not significant; N/R, not reported; SEER, Surveillance, Epidemiology, and End Results; MST, median survival time; GGO, ground-glass opacity.

Table 2 Evidence for survival after sublobar resection for cT1N0M0 NSCLC of 2 cm or less in size

Author [year]	No. of patients	Intentional *vs*. compromised	Mode of sublobar resection	5-YSR (%)	Local rec. rate (%)
Kodama [1997]	46 (<3 cm in size)	Intentional	Seg.	93.0	8.7
Okada [2001]	70	Intentional	Extended seg.*	87.3	0
Koike [2003]	74	Intentional	Wedge: 14; Seg.: 60	89.1	2.7
Fernando [2005]	124	Compromised	Wedge: 52; Seg.: 73	55.8 mo; (MST)	17.5
Okada [2006]	260	Intentional	Wedge: 30; Seg.: 230	89.6	4.9
Iwasaki [2007]	31	Mixed	Seg.	69.7	3.2
Sienel [2007]	32	Compromised	Seg.	68	12
Schuchert [2007]	182 (IA/IB)	N/R	Seg.	82	7.7
Bando [2009]	68	Mixed	Seg.	86.0	–
Watanabe [2009]	38	Intentional	Seg.	74.5	0
Wolf [2011]	154	Compromised	Wedge: 130; Seg.: 24	59	16
Donahue [2012]	40	Mixed	Seg.	68.8%, DFS	5

NSCLC, non-small cell lung cancer; 5-YSR, 5-year survival rate; Seg., segmentectomy; MST, median survival time; N/R, not reported; DFS, disease-free survival. *, Extended segmentectomy is defined as resection of both the affected segment and adjacent subsegments plus the exploration of mediastinal and hilar lymph nodes by intraoperative frozen sectioning.

Type of sublobar resection (segmentectomy versus wedge resection)

The most common operative approaches for sublobar resection are wedge resection and segmentectomy. Wedge resection consists of the removal of a lung tumor with a surrounding margin of normal lung tissue, and is not an anatomical resection. On the other hand, segmentectomy is an anatomical resection that usually includes one or more pulmonary parenchymal segments with the dissection of intraparenchymal and hilar lymph nodes. Segmentectomy theoretically has the advantages of a wider resection, reduced technical limitations for achieving adequate margins (57), and the more extensive resection of draining lymphatics including intersegmental planes that are commonly considered to be a source of residual cancer cells (58). Many reports have suggested that nonanatomic wedge resection is inferior to anatomic segmentectomy as an oncologic approach (9,59). Actually, these reports found a significant increase in local recurrence and a decrease in survival after wedge resection compared with segmentectomy for especially stage I NSCLC (*Table 3*) (50,60-63). The superiority of segmentectomy with regard to the parenchymal margin has been documented in prior studies (57,61). For example, a study from the University of Pittsburgh retrospectively reviewed 81 patients who were treated with sublobar resection. Among the patients with wedge resection, only 39% had a margin greater than 1 cm, compared with 73% of those with segmentectomy (61). Consequently, the incidence of local recurrence was significantly higher in the wedge resection group. A prospective study by Kent *et al*. reached a similar result that wedge resection had a significantly smaller surgical margin than segmentectomy for non-small lung cancer (57). The inadequate surgical margins in wedge resection would result in a higher incidence of local recurrence (64). Sawabata *et al*. (65) and Shuchert *et al*. (54) identified a margin distance of greater than 2 cm or greater than the maximal tumor diameter as favorable indicators of decreased local recurrence after lung resection.

With respect to radiologic findings, based on the advent of high-resolution CT or TSCT, the radiology-pathology correlation has been studied (19,21,66), and the radiologic appearance of the various histologic subtypes in lung cancer, especially adenocarcinoma, has been described in detail (67). It has been shown that the lesions with GGO are more likely to be "early" adenocarcinomas such as adenocarcinoma in situ (AIS), or minimally invasive adenocarcinoma (MIA). Recent studies demonstrated that patients with GGO-dominant lung adenocarcinoma (consolidation/tumor ratio ≤0.5 on TSCT scan; *Figure 1*) of clinical stage I have an excellent prognosis (19,68). These tumors might be curatively treated with sublobar resection such as wedge resection or segmentectomy.

Table 3 Outcome after wedge resection and segmentectomy for NSCLC

Author [year]	No. of patients	Stage	Compromised *vs.* intentional	Resection type	5-YSR		Local rec. rate (%)	
					Wedge	Seg.	Wedge	Seg.
Miller [2002]	25	≤1 cm	Compromised	Wedge: 13; Seg.: 12	27%	57%	30.8	8.3
Okada [2005]	158	IA (≤2 cm)	Mixed	Wedge: 35; Seg.: 123	85.7%	96.7%	N/R	N/R
El-Sherif [2007]	81	I	Compromised	Wedge: 55; Seg.: 26	N/R	N/R	14.5	3.8
Sienel [2008]	87	IA	Compromised	Wedge: 31; Seg.: 56	48%; cancer-related	71%; cancer-related	55	16
Koike [2014]	328	IA	Mixed	Wedge: 112; Seg.: 216	68.0%; disease-specific	91.3%; disease-specific	34	6.3

NSCLC, non-small cell lung cancer; 5-YSR, 5-year survival rate; Seg., segmentectomy; N/R, not reported.

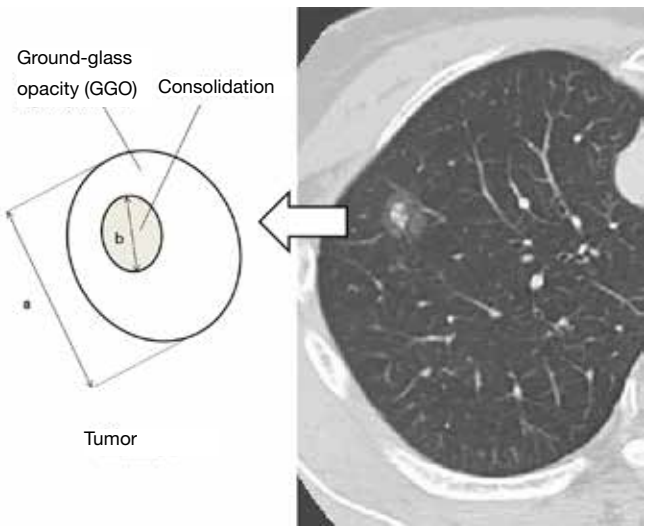

Figure 1 Calculation of the consolidation/tumor ratio to define radiologic noninvasive lung cancer on thin-section computed tomography. The maximum diameter of consolidation (b) is divided by the maximum tumor diameter (a) to give the consolidation/tumor ratio.

Intentional sublobar resection

Lobectomy has been the standard of care for early-stage NSCLC since the 1995 report from the LCSG (1). Many studies have retrospectively supported this result, and have indicated that lobectomy carries an overall and disease-free survival advantage when compared to sublobar resection (32,33,36,69). Consequently, sublobar resection has typically been used for high-risk, but still operable, patients with lung cancer. However, recent improvements in the detection of small peripheral tumors and GGOs associated with a favorable histology have led to the increased use of sublobar resection in many centers to include patients with an adequate physiologic reserve.

GGO is defined as a hazy increased attenuation with the preservation of bronchial and vascular margins on TSCT (70). It has been proposed that lung cancer with dominant GGO (consolidation/tumor ratio 0.5 or less) within the lesion is more likely to be an early form of adenocarcinoma such as AIS or MIA (19,21). In particular, some GGOs are accompanied by a solid part (consolidation), and it has been demonstrated that a consolidation represents the portion of invasive growth, i.e., the consolidation/tumor ratio is thought to predict pathologic early adenocarcinoma (21). On the basis of these observations, the Japan Clinical Oncology Group (JCOG) 0201 study (48), a multi-institutional prospective study, was planned to establish radiologic criteria for predicting pathologic early (noninvasive) adenocarcinoma. Based on the results of this study, radiologic noninvasive lung adenocarcinoma could be defined as an adenocarcinoma ≤2.0 cm (cT1a) with a consolidation/tumor (C/T) ratio of 0.25 or less. Subsequently, Asamura and colleagues (68) reevaluated the radiology-pathology correlation in the JCOG 0201 study in terms of the prognosis. The radiologic criteria of a C/T ratio of 0.5 or less in cT1a-b (≤3.0 cm) as well as 0.25 or less in cT1a (≤2.0 cm) could be used to define a homogeneous group of patients with an excellent prognosis after surgery. These criteria can be used to select patients with early lung adenocarcinoma in whom a sublobar resection such as wedge resection or segmentectomy would be safely indicated. Clinical phase II trials to determine the appropriateness of intentional sublobar resection for "early" adenocarcinoma with these radiologic criteria have been conducted (JCOG 0804 and JCOG 1211).

On the other hand, for radiologic invasive lung cancer (cT1aN0M0) with a tumor diameter of 2.0 cm or less and

a C/T ratio greater than 0.5, a prospective, randomized phase III study (JCOG0802/WJOG4607L) that compares lobectomy and segmentectomy in a noninferiority setting is ongoing (47). The primary and main secondary end-points are overall survival and postoperative pulmonary function, relapse-free survival, and proportion of local recurrence. This study began in August 2009 in Japan and a total of 1,100 patients will be accrued. Intraoperatively, the distance from the surgical resected margin to the tumor edge and lymph node must be evaluated. When lymph node metastasis is present or the resected margin is not cancer-free, the surgical procedure must be converted to a lobectomy. All randomized patients will be followed for at least five years. In North America, a similar trial entitled CALGB 140503 is also underway, in which the prognosis and preservation of pulmonary function are being compared in lobectomy and sublobar resection (segmentectomy or wedge resection) in a noninferiority study setting.

Postoperative pulmonary function

If we wish to advocate sublobar resection for early-stage lung cancer, it must offer some clinically significant advantage in comparison to lobectomy. The preservation of pulmonary function is one such meaningful advantage. Theoretically, sublobar resection such as segmentectomy has an anatomically functional advantage over lobectomy, since some segments of lung parenchyma that would otherwise be removed by lobectomy can be preserved. However, it is unclear whether the functional advantage of segmentectomy is as great as its anatomic advantage over lobectomy. In the 1995 LCSG trial (1), a preservation of pulmonary function was demonstrated for patients who underwent sublobar resection compared with lobectomy at 6 months after surgery, but not at 8 or 12 months. However, this may have been due to the loss of follow-up pulmonary function tests for many patients at this longer interval evaluation. Nevertheless, the increasing body of evidence of comparable prognostic outcomes between lobectomy and sublobar resection for small tumors has prompted surgeons to more exhaustively investigate their impact on postoperative pulmonary function (17,30,71). Takizawa and colleagues (72) retrospectively studied pre- and post-operative pulmonary function [forced expiratory volume in 1 second ($FEV_{1.0}$) and forced vital capacity (FVC)] in 40 segmentectomy patients and 40 paired lobectomy patients, who were matched with respect to the estimated propensity score. The significant benefit in $FEV_{1.0}$, but not that in FVC, as a percentage of the preoperative value, observed two weeks postoperatively in the group of patients who had undergone segmentectomy (segmentectomy group 73.0% versus lobectomy group 66.6%, P=0.03) was maintained at 12 months (segmentectomy group 93.0% versus lobectomy group 87.3%, P=0.03). Harada and colleagues (73) analyzed pulmonary function tests preoperatively and at 2 and 6 months after segmentectomy in 38 patients and after lobectomy in 45 patients, where both groups could tolerate a lobectomy and had clinical T1N0M0 NSCLC ≤2 cm. In the segmentectomy group, the postoperative reductions in FVC and $FEV_{1.0}$ were significantly smaller than those in the lobectomy group. On the other hand, a recent report by Deng and colleagues (74) failed to find a significant difference in the effect on pulmonary function after segmentectomy or lobectomy. Since these results were mainly derived from retrospective studies, the preservation of postoperative pulmonary function with sublobar resection should be confirmed in a prospective study based on adequate postoperative follow-up pulmonary function data.

Conclusions

The number of patients who present with small tumors continues to increase due to the prevalence of CT screening. This should lead to a notable increase in the detection of tumors smaller than those included in the LCSG trial (1), which was conducted in the 1980s and based on the detection of lung cancer by plain chest radiography. Additionally, a recent report from the National Lung Screening trial demonstrated that CT screening for lung cancer reduced relative lung cancer mortality compared with screening by chest radiography (75). Sublobar resection will be expected to play an important role as a primary treatment option for patients with small stage IA NSCLC, especially if 2 cm or less in size, who can tolerate a lobectomy. However, care should be taken in promoting widespread indications for intentional segmentectomy in good-risk patients with a small tumor until the results of ongoing prospective, randomized clinical trials, such as JCOG0802/WJOG4607L and CALGB140503, are available (47). If these trials demonstrate that lobectomy and sublobar resection have similar curative effects and that sublobar resection offers better pulmonary functional preservation, sublobar resection should take the place of a lobectomy as the standard of care for patients with early-stage NSCLC.

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Footnote

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Is surgery still the best management option for early stage NSCLC?

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Abstract: Under the formidable thrust of alternative management options for early stage lung cancer, the role of surgery in this disease subset has been questioned. Stereotactic body radiotherapy (SBRT) has been advocated as an ideal substitute for surgery not only in high risk patients or for the ones who refuse surgery but also in lieu of sublobar resection in otherwise fit patients. The therapeutic modalities for early stage NSCLC were compared as to warranting local control, enabling adequate tissue sampling for biomolecular studies, and effecting optimal pathologic staging while saving lung parenchyma. As a result, surgery still remains the best management option for early stage lung cancer in 2014.

Keywords: Lung cancer; surgery; stereotactic body radiotherapy (SBRT)

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Introduction

Nowadays, modern clinical outcomes and cost-effectiveness issues mandate careful attention to the process flow governing the diagnostic and therapeutic pathways in lung cancer management (1). Best practice protocols, like Proven Care, are characterized by the focus on the diagnostic and therapeutic value of surgery as the central modality in managing early as well as locally advanced NSCLC (1). Indeed, surgery has been considered for decades the ideal therapeutic option mainly to ensure optimal local control of the disease. The aim of this paper is to demonstrate that minimally invasive thoracic surgery (MITS) remains the best management choice for early NSCLC because, besides continuing to warrant best local control, it is crucial to provide tissue for biomolecular studies and effect the best pathological staging while preserving lung parenchyma (2,3).

Local control

One of the advantages of surgical treatment for early stage NSCLC includes local control of the disease. Recurrent tumors may be present at different sites after initial surgery. In this setting, and unlike many of the series based on other modalities of local control of NSCLC, the surgical series are characterized by a precise definition of the concept of local recurrence (1). In case of local recurrence, tumors may involve adjacent lung parenchyma, the bronchial stump, or the hilum adjacent to the bronchial stump (4). Regional failure means that recurrence is located in the hilum separate from the bronchial stump, mediastinum, chest wall or the ipsilateral pleura (4). When distant failure is present, tumor occurs in the separate lobe of the ipsilateral lung, contralateral thorax, supraclavicular lymph nodes or in a distant organ (4). According to ACOSOG Z0030 trial conducted among 578 pT1 and 440 pT2 patients with recurrent early stage NSCLC, the median overall survival (OS) for pT1 tumors was 9.1 years and 6.5 years for pT2, respectively (4). The 5-year disease free survival was 77% for pT1 and 58% for pT2, respectively whereas the 5-year local disease-free survival was 95% for pT1 and 91% for pT2, respectively (4). When the patterns of recurrence were considered, local recurrence was observed in 1% and 3% of T1 and T2 tumors, respectively (4). Moreover, regional and combined local and regional recurrences were seen in 4% and 0.4% for T1, and, 3% and 0.7%

for T2 subsets, respectively (4). Conversely, randomized trials of stereotactic body radiation treatment like RTOG 0236 do not generally provide a detailed breakdown of the recurrence sites and fail, at this point in time, to prospect 5 year survival figures (4). The fact that stereotactic body radiotherapy (SBRT) remains a promising modality for local control of NSCLC is demonstrated by the 91% and 87% 3-year local and loco-regional recurrence free survival rates observed in RTOG 0236 (4). Even in large retrospective series, the local and regional recurrence rates at 2 years after SBRT were 4.9% and 7.8%, respectively (5). In the same study from the Netherlands, the corresponding local and regional recurrence rates after 5 years were 10.5% and 12.7%, respectively (5). The difference in local and regional relapse compared to the results from ACOSOG Z0030 trial is particularly significant if one considers that 65% (441 patients out of 676) in the SBRT retrospective study did not have a pre-treatment histological diagnosis of lung cancer (5). A direct comparison of the available treatment modalities to attain local control of early stage lung cancer was published by the MD Anderson Cancer Center in 2012 (6). Overall, more than 10,000 patients with stage I NSCLC older than 66 years (median age, 75 years) were considered (6). Among the possible treatment options, lobectomy, sublobar resection, SBRT, conventional radiation, and, observation were evaluated and the main conclusion was that lobectomy yielded the best overall and disease-specific survival rate after 6 months (6). A caveat to the interpretation of the results was suggested by the limited number of SBRT patients in a retrospective series which were nevertheless analyzed with the propensity score method (6). However, SBRT was related to the best mortality rate within 6 months of treatment (6).

Tissue for biomolecular evaluation

One of the most intriguing perspectives of biomolecular medicine is the possibility of diagnosing lung cancer on blood samples (7,8). Recently, Sozzi and coworkers in the MILD lung cancer screening trial have demonstrated that combining screening with low dose CT (LDCT) scan and miRNA signatures the rate of false positives can be reduced fivefold, thus limiting the resort to unnecessary surgery (9). Theoretically, blood-based diagnosis would facilitate targeted treatment especially in patients with lung cancer relapses or convey reluctant or inoperable patients towards non-surgical therapies with the certainty of a histological type. However, the recent reports of increasing resistance to targeted drugs emphasize the concept of multiclonality within the same tumor mass (10). Accordingly, only representative samples from a tumor mass could ensure adequate genomic profiling in the perspective of targeted treatment. The role of surgical biopsies in this context seems obvious especially if tumor resistance is to be ascertained and avoided. Likewise, the question arises as to whether circulating tumor cells or DNA can replace the diagnostic accuracy of surgical specimens in the future (11). In this setting, next generation sequencing (NGS) platforms can be applied to circulating cells as well as free DNA and are already showing promising results (12). However, since most mutations in tumor DNA do not contribute to oncogenesis and are transient, the clinical impact of NGS platforms is yet to be understood (12). Sizeable samples may still be necessary in order to distinguish driver from transient mutation (12). In the meantime, costs and disadvantages of NGS platforms represent the hurdles to be overcome for a more widespread use of this technology (12).

In this setting, the detection of areas in the airways prone to develop recurrences in close contiguity to resected lung parenchyma or after definite time frames from previous pulmonary resection is intriguing because biomolecular studies seem to show the potential to orient the clinical surveillance by analyzing modulation of genetic expression in the bronchial epithelium (13).

Correct staging

Adequate patient selection is crucial to obtain long-term results when any local modality of lung cancer treatment is used. In this context, correct clinical and pathological staging represents a tenet of modern thoracic surgery. Guidelines have proposed to effect standardized protocols for both preoperative and intraoperative staging (14). The quest for the identification of subsets of mediastinal nodal involvement amenable to primary surgery has provided important practical consequences (15). As an example, in Europe, occult as well as single station N2 NSCLC are now increasingly considered a surgical disease given the encouraging survival rates reported in surgical series (15). Minimally invasive techniques, especially VATS, enable surgeons to solve clinical dilemmas with staging procedures which can be performed under locoregional anesthesia (3,16,17). Operations effected via single port (uniportal) VATS are used to distinguish between T2 and T3 or N2 and N3 when EBUS and mediastinoscopy are not helpful or cannot be technically carried out. In the

setting of prethoracotomy exploration of the mediastinum, video assisted mediastinal lymphadenectomy (VAMLA) and trascervical extended mediastinal lymphadenectomy (TEMLA) represent another example of single port surgery which can be used to better select surgical candidates for lung resection (18,19). The whole staging-based prognostic infrastructure of oncologic treatment modalities is the guiding principle for the selection of surgery for early stage lung cancer (20). Without histological confirmation, only clinical stages can be compared between treatment yielding an apparent outcome equipoise (21); this is particularly relevant if one thinks that regional failures after SBRT may account to 15% and mediastinal failures can be found in 7.5% of the patients originally treated with ablative radiation (22). To further complicate this issue, it has been reported that histological confirmation of lung cancer patients treated with SBRT is needed in only 35% of the patient population (5). To justify this paradigm shift not yet supported by conventional collected evidence (i.e., prospective, randomized trials-see above), a theoretical pathway leading to SBRT-led treatment of early stage lung cancer has been put forward which includes ad hoc interpretation of current guidelines, PET driven decision analysis, extremely conservative estimate of patients' preoperative cardio-respiratory reserve or the adoption of somewhat vague and unconventional terminology (i.e., pulmonary insufficiency) when defining operability, and the accidental inattention to thoracic surgical input into tumor boards (5,23,24). However, the quality issues in SBRT administration are partially counterbalanced by similar pitfalls of surgical treatment. Indeed, advocates of SBRT emphasize the non homogeneous quality of surgery outside clinical trials, especially in terms of intraoperative nodal sampling or dissection (25). The thoracic surgical community is taking action and a more rigorous attitude towards mediastinal lymphadenectomy is currently advised (26).

The meaning of minimally invasive thoracic surgery (MITS)

As surgeons, we are concerned with offering the best possible procedure to our patients in order to obtain the longest recurrence free survival (27). In this context, sublobar resections are under scrutiny for their oncologic efficacy compared to SBRT as an alternative to lobectomy for early stage lung cancer (28,29). In particular, wedge resection have been considered by some authors a sort of palliative surgical procedure which should be replaced by anatomical segmentectomy with nodal dissection as the procedure of choice for stage IA NSCLC (27). Again, a matter of quality in surgery has been raised, with regard to the tumor-free margins attainable during non-anatomical segmentectomy, i.e., lung wedge resection (27). Be as it may, correct indications for wedge resection still remain and include CT screened small, subcentimetric nodules and ground glass opacities (GGOs) especially when the solid component is less than 25% compared to the ground glass counterpart (30). In addition, authoritative institutions have reported no differences in survival between sublobar (including wedge resections) and lobectomy for solid nodules classified as clinical stage IA NSCLC (31).

Conclusions

One shared statement that depicts the current surgical philosophy towards lung cancer is expressed in the recent Society of Thoracic Surgeons' recommendations on the role of surgeons in the lung CT screening programs (30). Modern surgery for early stage lung cancer needs to focus on "the least parenchymal resection compatible with current diagnostic and oncologic principles performed through the least invasive surgical approach" (30). By respecting this fundamental principle, surgery remains in 2014 the best management option for early stage lung cancer.

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Footnote

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Treatment of Pulmonary Nodules

Cons: long-term CT-scan follow-up is not the standard of care in patients curatively treated for an early stage non-small cell lung cancer

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Introduction

About 25% of patients with early stage (I, II, IIIA non-N2) non-small cell lung cancer (NSCLC) qualify for a treatment with curative intent, consisting of either radical surgical resection or radical radiotherapy. The former consists of at least an anatomical lobectomy, the latter is nowadays mainly given at ablative doses with stereotactic techniques (SABR). Radically treated patients may develop either locally or distantly relapsing lung cancer, or a second primary (lung) cancer. Besides, they retain a significant excess conditional mortality with an increasing relative contribution of cardiovascular and respiratory co-morbidity (1). Recurrence dynamics of resected early-stage NSCLC displays a multi-peak pattern, which supports the hypothesis of a metastasis growth model previously described for early-stage breast cancer (2). An initial surge in the hazard rate 9 months after surgery, is followed by two smaller peaks at the end of the second and fourth years, respectively (*Figure 1*). This pattern is dominated by distant metastatic events which decrease over time and are virtually absent after 5 years. Two distinguishable peaks are noted for local recurrence in the first and second years, but this is rare thereafter. The risk of local or distant recurrence is 10%~38%, mainly dependent of stage and highest in pII-III NSCLC. This risk can be moderately reduced by the administration of postoperative platinum-based chemotherapy, with an average increase in 5-year survival of 5% (3). In contrast, the hazard rate for second primary lung cancer exhibits a more uniform pattern over time, is 1% to 4% per patient per year in most series (4) and increases even after 5 years. The median time interval between the two tumours is 14.5 months (5,6). Lastly, these patients are at risk of developing a second primary non-respiratory cancer: the most frequently diagnosed tumours are located in the head and neck and the urinary tract.

The outcome of recurrent lung cancer depends on the type of recurrence, its stage at diagnosis and residual functional treatment capacity. The stage of a second primary lung cancer is the strongest predictor of survival (7). Whereas the treatment of distant metastatic disease is palliative, some patients with loco-regional recurrence or second primary cancer benefit from a second curative treatment, either by resection or by SABR. This is highly dependent of the residual pulmonary function after the first treatment and cardiac co-morbidity. Only a fraction of patients with early stage recurrence are hence benefiting from a surveillance strategy.

Using a systematic postoperative surveillance protocol using CT and chest X-ray (CXR) over a 5-year period, 19 second primary lung cancers were diagnosed among 124 patients who had undergone previous resection, of

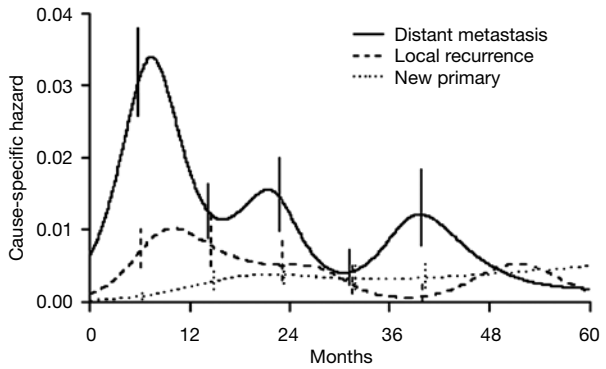

Figure 1 Cause-specific hazard rate estimates for local recurrence, distant metastasis, and second primary in 1,506 patients undergoing surgery with curative intent for early-stage non-small-cell lung cancer [copyright with permission of (2)]. Hazard rate obtained by the piecewise exponential regression approach. Vertical lines represent 95% pointwise confidence intervals.

Table 1 5-year survival after a new resection due to recurrence after complete curative resection of non-small cell lung cancer

Study	Local recurrence (%)	Second primary lung cancer (%)
Voltolini *et al.* (10)	15.5	25-52.5
Hamaij *et al.* (11)		60.8
Rosengart *et al.* (12)		38
Hung *et al.* (13)	15	

whom 74% underwent a curative second resection (8,9). The 5-year survival of patients undergoing a reoperation for a second primary was between 25%~60% (10-12) (*Table 1*). Only 1 of 9 isolated local recurrences was resectable, even though 8 of 9 recurrences were asymptomatic at the time of detection. Voltolini *et al.* reported that 5-year survival after reoperation for locally recurrent bronchogenic carcinoma was 15.5% (10). The 5-year post-recurrence survival in another series of patients undergoing reoperation after local recurrence was also 15% (13). In resected stage I NSCLC with local recurrence, a second surgical resection had a more favourable survival [hazard ratio (HR) 0.089)] than with chemotherapy and/or radiotherapy (HR 0.326) and without treatment (HR 1.0, reference; P=0.001) (6,14). In early stages of recurrent or secondary lung carcinoma, even higher local control and overall survival rates can be achieved by complete pneumonectomy, with 5-year survival of about 50% in stage I and 40% in stage II carcinoma (15).

Short term surveillance after radical lung cancer treatment

Opinions differ and evidence is only moderately strong regarding the intensity and duration of surveillance strategy in the first years after a radical treatment. Resection rates for local-only initial recurrence of 33% and 70% are reported using CT for surveillance compared with 37.5% using CXR. Other series report resection rates for metachronous tumors of 63% and 75% using surveillance by CXR. *Table 2* lists the available guidelines and recommendations with their grade of evidence. Some recommendations even change grade without proper new evidence, reflecting their expert's rather than evidence-based decision process. Whereas most guidelines agree on periodical history, physical exam and CXR, variation is present on the frequency of chest CT-scan, varying from none over 4 monthly to yearly for life. We know that CT-scan is superior to CXR in the follow-up of patients after curative resection of lung cancer (22). Recurrences at the post-resection site were detected by CT-scan with a 94% sensitivity and 87% specificity, and a negative predictive value of 99%. Positive predictive value was only 53%. The abovementioned variation in surveillance intensity can be explained by differences in the reported outcomes, varying from detection of early recurrence over resectability, outcome and toxicity or complications of treatment. For second primary lung cancer, a better 5-year survival rate was reported in patients in whom a CT-scan surveillance was installed (18). In a retrospective cohort study using Surveillance, Epidemiology and End Results (SEER)-Medicare data to determine the imaging study used between 90-365 days following surgical resection in stage I-IIIA NSCLC between 1998 and 2009, the comparative effectiveness of CT-scan *vs.* CXR surveillance was explored in terms of overall survival (OS), using a stratified Cox model based on stage and adjusted for age, gender, race, census median income, Charlson comorbidity index, and adjuvant chemotherapy (23): 5,968 (54%) patients were followed by CT, and 5,083 (46%) by CXR. Patients with earlier stage, older age, and lower census median income were less likely to undergo CT surveillance. CT surveillance increased over the study period from 23% in 1998 to 68% in 2009. In the analysis of surveillance modality and OS, a significant interaction was identified between imaging and diagnosis year (P<0.001). The effect of CT surveillance on OS steadily improved over time, and was significantly better than CXR in the most recent time periods of study.

The schedule of follow up should be ideally modelled to

Table 2 Guidelines on surveillance after curative resection

Organization	Years	Follow-up	Grade of recommendation
National Comprehensive Cancer Network (16)	Year 1 and 2	History, physical examination, and CT every 4-6 months	IIB
	Year 3 to 5	History, physical examination, and CT every 12 months	
	Year 5 and later	History, physical examination, and CT every 12 months	
American Association for Thoracic Surgery (17)	Year 1 to 3	CT every 6 months	None
	Year 4	CT every 12 months	
	Year 5 and later	CT every 12 months	
American College of Chest Physicians (18)	Year 1 and 2	History, physical examination, with CXR, or CT every 6 months	IIC
	Year 3 to 5	History, physical examination, with CXR, or CT every 12 months	
	Year 5 and later	History, physical examination, with CXR, or CT every 12 months	
American Society of Clinical Oncology (19)	Year 1 and 2	History, physical examination, every 3 months	None
	Year 3 to 5	History, physical examination, every 6 months	
	Year 5 and later	History, physical examination, every 12 months	
European Society of Medical Oncology (20,21)	Year 1 and 2	History, physical examination and CT-scan every 6 months	IIC and IIIB
	Year 3 and later	History, physical examination, and CT every 12 months	

CXR, chest X-ray.

cluster follow-up visits within recurrence peaks at 9 months, 2 and 4 years, to detect events at a time when they may be treated with curative intent (2). Most series do not report on quality of life or other patient-related outcomes. Walsh *et al.* illustrated that screening for asymptomatic recurrent lung cancer is unlikely to be cost effective (6). A French randomized study is currently addressing the issue of the intensity of surveillance during the first years post radical treatment (clintrials.gov NCT00198341). Pending these results, it is probably best to have at least one chest CT-scan performed within the first postoperative year in patients considered fit for further radical treatment.

Long term surveillance after radical lung cancer treatment

The issue whether surveillance should arbitrarily stop 5 years after treatment is increasingly challenged by recent data on lung cancer screening by low dose spiral CT-scan in a risk population of (ex-)smokers (24). Low-dose CT-scan seems to be comparable to standard-dose CT with regard to the identification of recurrent disease. The National Lung cancer Screening Trialists (NLST) found a 20 percent lower lung cancer mortality among trial participants screened with low-dose helical CT relative to CXR. In the randomized NELSON lung cancer screening trial using low dose spiral CT-scan, 5-year lung cancer survivors are eligible for enrolment in view of their increased risk of second primary lung cancer (25). Data on the prevalence of participants with a second primary cancer and their outcome are awaited.

Long term follow up of curatively treated early lung cancer patients is increasingly becoming an issue now that CT-scan screening will detect more patients in an early stage in whom survival is high and who are, independently of their smoking status, at risk of developing a second primary lung cancer 5 or more years after their first one. Although the data of the NLST are compelling and invite to implementation to the population of radically treated patients, several caveats argue against blind extrapolation:

(I) NLST and NELSON participants had to be eligible for radical resection. Increasing comorbidity and functional impairment by a previous resection will render patients less fit for surgery. Although SABR or sublobar resections could replace the standard anatomical lobectomy in lesser fit patients, their equivalence is still debated (26,27);

(II) Cost effectiveness (CE) of lung cancer screening in a risk population is estimated to be 81,000 $/QALY with the number of CT-scan being the main cost driver (28). As the incidence of non-calcified nodules in the population of radically treated NSCLC is likely higher than in the NLST, the number of

confirmatory conventional dose CT-scan will be higher, negatively influencing the CE balance;

(III) Other drivers of CE of screening with low dose spiral CT are age, smoking status and gender. It is unclear whether the population of radically treated NSCLC will match with the NELSON and NLST population for these characteristics, making assumptions about the non-inferiority of low-dose CT-scan in survivors of lung cancer unlikely;

(IV) How the CT-scan is interpreted also will have an effect. For instance, if radiologists use the new American College of Radiology Lung RADS reporting system, the false positivity rate will decrease by about 50% and could substantially decrease the number of follow-up CT-scan required, at the cost of sensitivity (29);

(V) We should be aware that not all screen detected lung cancers are in an early stage. A screening CT-scan looks for non-calcified pulmonary nodules in an asymptomatic at risk population while a diagnostic CT-scan is performed in a person who has a sign or symptom of disease. There is also the risk of unnecessary invasive studies and therapy for "overdiagnosed" lung cancer. Observational studies of screening for lung cancer with low-dose CT that preceded the NLST trial have estimated the extent of overdiagnosis to range between 13 and 27 percent (30,31).

Conclusions

Pending the answers to these questions, it is hap hazardous to embark on a routine follow-up with low dose CT-scan beyond 5 years in all radically treated lung cancer patients. We recommend an international effort to draft and accrue participants in a large scale randomized trial comparing long term surveillance with periodic low dose spiral CT-scan versus a to be agreed standard follow-up, which could consist in simple follow up with or without CXR.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Treatment of Pulmonary Nodules

Pros: After stereotactic ablative radiotherapy for a peripheral early-stage non-small cell lung cancer, radiological suspicion of a local recurrence can be sufficient indication to proceed to salvage therapy

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Introduction

Stereotactic ablative radiotherapy (SABR), also known as "stereotactic body radiation therapy" (SBRT), has revolutionized the treatment of early-stage non-small cell lung cancer (NSCLC), providing an effective treatment option for medically-inoperable patients. Modern advancements in the planning and targeting of radiotherapy have allowed SABR to deliver ablative doses as high as 150 Gy (when converted to 2 Gy per fraction) in a precise and highly conformal manner (1). After SABR, rates of primary tumor control are excellent, in excess of 90% at 5 years (2). These promising results have led to suggestions that SABR may be comparable to the historic gold standard, surgical resection, as first-line treatment in operable patients. Three randomized control trials (RCTs)—the STARS trial, the ROSEL trial and ACOSOG Z4099—attempted to compare SABR and surgical resection, but all closed prematurely due to insufficient enrollment. A pooled analysis of the patients accrued to STARS and ROSEL suggested that, at a minimum, there was equipoise between the two treatments, with significantly better overall survival demonstrated in the patients receiving SABR (3). More robust RCT evidence is still awaited, and at least two RCTs examining this question are ongoing including the STABLE-MATES and SABR-Tooth trials (4).

Although SABR has been widely adopted over the past decade (5), there is ongoing uncertainty in assessing treatment response and detecting local recurrence (LR). Following SABR, radiation-induced lung injury (RILI) is common, which manifests as local changes to the lung parenchyma on CT imaging that are usually asymptomatic. Both acute (within 6 months) and late (after 6 months) changes have been previously described and can obscure the detection of residual and recurrent disease (6). Acute changes have been categorized as one of 4 types: diffuse consolidation, patchy consolidation, diffuse ground-glass

opacities, or patchy ground-glass opacities. Late changes typically manifest as a modified conventional pattern, mass-like fibrosis or scar-like fibrosis (7). The possible mass-like appearance of RILI is likely a product of the highly conformal treatment (8), and this appearance may mimic the growth pattern of locally recurrent disease. Benign CT changes may continue to evolve in morphology and severity up to 2 years following SABR (7), which can further impair the detection of LR during the critical period of time when LRs are most likely to occur (9). Predicting which cases of RILI may be at increased risk of recurrence is also challenging, with initial response to treatment and rate of tumor shrinkage not being associated with ultimate local control (10).

Some patients who develop LR after SABR may be candidates for salvage treatments, including surgical resection or repeat SABR (11). Accurate and early detection of LR following SABR is a critical first step to ensuring that recurrences are managed efficiently. For patients with imaging findings suspicious for LR, we argue that radiologic evidence of recurrence can be sufficient to detect LR, and that patients should not be denied the option of salvage treatment if a biopsy is unsafe or contraindicated.

Biopsy: proceed with caution

Ideally, all salvage treatment decisions would be informed by a definitive pathologic diagnosis. The reality, however, is that lung biopsies are imperfect investigations, they are associated with a risk of complications, and pathologic interpretation can be difficult when sampling an irradiated area. Even in patients who have not undergone radiation in the past, the performance characteristics of CT-guided biopsies may be suboptimal. In a retrospective analysis of 242 patients, CT-guided fine needle aspiration biopsies (CT-FNAB) failed to achieve a definitive diagnosis in 20% of cases (inadequate tissue) compared with only a 3% non-diagnostic rate with CT-guided core biopsies (CT-CB) (12). Although highly specific (99.1%), CT-CB are prone to false negatives, with a reported negative predictive value of only 73.3% (13). Furthermore, the accuracy of CT-CB appears to worsen in lung lesions <1.5, >5 cm (increased extent of necrosis) and those with a benign histology (14). A meta-analysis of 32 studies revealed that CT-CB and CT-FNAB have high overall complication rates of 39% and 24% respectively. The bulk of these events were termed "minor complications", however, they are not negligible sources of morbidity as they included transient hemoptysis and pneumothorax not requiring intervention. Major complications, including pneumothorax requiring intervention and hemothorax, occurred at a rate of 5.7% with CT-CB and 4.4% with CT-FNAB. The overall pooled risk of any pneumothorax was 25% for CT-CB (15). In radiated lesions, accurate assessment of biopsy specimens may be further obscured by fibrotic and necrotic changes. In one report, a patient required 11 needle passes over 3 different biopsy attempts before a diagnosis of recurrence was made (16).

Recurrence versus fibrosis: a non-invasive approach

The limitations of biopsy, including the performance characteristics, risks of complications, and difficulty with interpretation, suggest that they should only be pursued when there is a high likelihood of the biopsy results changing management.

Recent studies have demonstrated that CT imaging findings, termed high risk features (HRFs) (*Table 1*), can be useful without biopsy to identify LR. The HRFs were first evaluated by Huang *et al.*, who conducted an analysis to determine the performance characteristics of these features. Their study matched 12 patients with biopsy-proven recurrence to 24 patients without recurrence, and found that several of the HRFs were significantly associated with LR. The top performing HRFs, with both a sensitivity and specificity over 80%, were: growth after 12 months, bulging margins, and craniocaudal growth, which was a newly identified HRF in that study. Although several HRFs had good sensitivity and specificity when considered individually, the presence of multiple features in a single patient (≥3 features) achieved superior results with excellent specificity and sensitivity scores of >90% (17). Most of the HRFs (all except for loss of linear margin) were subsequently validated in a separate, independent study, and similar performance characteristics were demonstrated. With separate validation completed, these HRFs should be considered appropriate for clinical use (18).

In patients with a suspected LR, FDG-PET may be useful as an adjunct to the CT-based HRFs, although its role is not as well-defined. Using FDG-PET scans to help distinguish between fibrosis and LR is confounded by the risk of false positives due to the increased metabolic activity related to RILI. Several studies have reported, however, that using a threshold SUV_{max} of ≥5, or greater than SUV_{max} prior to treatment, may be a more reliable predictor of LR (6).

Table 1 Previously reported high risk CT features predictive of local recurrence [initially reported by Huang *et al.* (17) and validated by Peulen *et al.* (18)]

High risk feature	Sensitivity (%)		Specificity (%)		P value[†]	
	Huang *et al.*	Peulen *et al.*	Huang *et al.*	Peulen *et al.*	Huang *et al.*	Peulen *et al.*
Enlarging opacity	92	100	67	31	<0.001	0.035
Sequential enlarging opacity	67	62	100	77	<0.001	0.033
Enlarging opacity >12 months	100	92	83	50	<0.001	0.013
Bulging margin	83	85	83	100	<0.001	<0.001
Loss of air bronchogram	67	15	96	100	<0.001	0.105
Linear margin disappearance	42	85	100	100	0.002	<0.001
Craniocaudal growth	92	100	83	50	<0.001	0.001
Unilateral pleural effusion	–	31	–	96	–	0.035
Relative growth	–	85	–	65	–	0.001

[†]P<0.05 were considered significant.

Conclusions

Ongoing challenges in accurately distinguishing between LR and RILI on follow-up imaging have complicated decision-making regarding salvage therapy. Biopsies may establish a definitive diagnosis, but at a significant risk of morbidity and inaccurate results, demanding careful consideration regarding their use. HRFs are a validated tool that can indicate a high risk of recurrent disease. Indeed, even in the setting of a newly diagnosed, untreated pulmonary nodule, several guidelines suggest that proceeding to treatment without a biopsy is an appropriate approach when the risk of malignancy is high (19,20), and it is reasonable to extend that paradigm to the post-treatment setting.

For patients who have the option of undergoing biopsy, the available evidence suggests that in the presence of radiologic evidence highly suggestive of LR (e.g., ≥3 HRFs), the pre-test probability of malignancy is sufficiently high that the risk of biopsy likely outweighs any potential benefits. In these situations, a negative biopsy would not be expected to be sufficiently reassuring that there is actually no recurrence present.

For cases where a biopsy is not possible due to significant comorbidities, patient refusal, or an inaccessible lesion, proceeding to salvage therapy based on strong radiologic findings alone is reasonable, as the alternative (i.e., continued observation) puts the patient at risk of progression and metastases.

For all cases, we recommend discussion at a multidisciplinary tumour board to aid with decision-making, and all decisions need to be made in conjunction with the patient after weighing the risks and benefits of the different options.

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Footnote

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Image-guided techniques for localizing pulmonary nodules in thoracoscopic surgery

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Abstract: Low-dose computed tomography (LDCT) screening has increased the detection rate for small pulmonary nodules with ground-glass opacity (GGO) in the peripheral lung parenchyma. Minimally invasive thoracoscopic surgery for these lung nodules is challenging for thoracic surgeons, and image-guided preoperative localization is mandatory for their successful resection. Image-guided localization methods primarily include two imaging tools: computed tomography (CT) and bronchoscopy. These different methods may use different localized materials, including hookwires, dyes, microcoils, fiducial markers, contrast media, and radiotracers. Ultrasonography and near-infrared imaging are also used for intraoperative localization of lung lesions. In this article, we review different localization techniques and discuss their indications and limitations.

Keywords: Computed tomography (CT); electromagnetic navigation bronchoscopy; pulmonary nodule; video-assisted thoracoscopic surgery (VATS)

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Introduction

Lung cancer screening using low-dose computed tomography (LDCT) has been proven to reduce lung cancer mortality as well as all-cause mortality in high-risk patients, with a lung cancer detection rate of around 3% (1-4). Therefore, LDCT is accepted as an effective lung cancer screening tool for high-risk patients. However, 23%~27% of the screening population has screening-detected indeterminate lung nodules and may need further management (5,6). Although there is no definitive gold standard for such management, several guidelines are available for the management of lung nodules found during LDCT screening (7-9). Nodule size, growth, and size of the solid component may predict the possibility of malignancy, and surgical biopsy for histological determination is required for patients with nodules that have a high possibility of malignancy (7-9).

With the advancements made in video-assisted thoracoscopic surgery (VATS) in recent decades, thoracic surgeries are increasingly performed using VATS because of similar long-term survival outcomes, better cosmetic results, shorter hospital stays, and less tissue injury compared with those for open surgery (10-12). Recently, uniportal VATS for major lung resection revolutionized the treatment of lung tumors (13-16). Gonzalez *et al.* reported the first uniportal VATS lobectomy in 2011 (13). Since then, more complicated procedures, including segmentectomy, pneumonectomy, tracheal resection, anastomosis, and even pulmonary vascular reconstruction, have been performed using uniportal VATS (14,16). Compared with those complicated thoracic surgeries, it may be more difficult to perform minimally invasive surgery for LDCT-detected nodules. These nodules are thoracoscopically invisible and

impalpable with VATS. Therefore, VATS for these small, partially solid nodules with ground-glass opacity (GGO) is a challenge for thoracic surgeons. Accurate and effective preoperative or intraoperative localization techniques are helpful for successful VATS tumor excision and have become even more important than they were in the past.

Several localization methods have been described for small pulmonary nodules. The characteristics of an ideal localization technique include: (I) a high accuracy rate; (II) a low morbidity rate; (III) minimal patient discomfort; (IV) a short procedure time; (V) the ability to be applied to the whole lung field; (VI) the use of techniques that are available in most institutes with low additional equipment-dependent requirements; (VII) cost-effectiveness; (VIII) no radiation exposure to either the surgeon or the radiologist; and (IX) no need to transport the patient from the area in which the nodules are localized to the operating room. Recently, several studies have reported the efficacy and accuracy of performing localization in a hybrid operating room (17,18). Currently, there are many different localization methods available that use different guided systems and localized materials, and each has its advantage and disadvantages. Image-guided localization methods include two mainstream imaging tools: computed tomography (CT) and bronchoscopy. These different methods may use different localized materials, including dyes, hookwires, microcoils, metallic fiducial markers, contrast media, and radiotracers. Ultrasonography and near-infrared imaging are also used for intraoperative localization of lung lesions. In this article, we review the current commonly used localization techniques, as well as novel techniques for VATS lung nodule excision, and discuss the advantages and disadvantages of these techniques.

CT guided techniques

Hookwire localization

Localization with hookwire placement is the oldest and probably the most common method of nodule localization (19). The conventional mammographic hookwire system is most commonly used. The wire is usually placed just before the patient is sent to the operating room in order to avoid the patient's discomfort and complications, such as wire dislodgement and pneumothorax. Advantages of this method include an acceptable successful localization rate (93.6–97.6%) and a short localization duration (19-26). Additionally, surgeons can visually identify the localized site directly without intraoperative fluoroscopy and radiation exposure.

Hookwire dislodgement from a perinodular location is the major drawback of this method, and it may lead to the loss of any intraoperative reference to the tumor location. The reported dislodgement rate is 2.4%~6.9% (20-26). Dislodgement may occur in three conditions during localization and surgery: when the patient is transported to the operating room, when the lung is deflated before surgery, and when the surgeons manipulate the lung during surgery. Therefore, surgeons should be very careful in such conditions to avoid dislodgement. Miyoshi *et al.* reported their modified method using a shorter, 1-cm-long hookwire with a firmly attached 30-cm-long 5-0 monofilament nylon suture (24). This method is more similar to microcoil placement with a suture, and it may reduce the incidence of dislodgement. Although initial localization failure was been noted in eight patients (8/125, 6.4%), all missing lesions and one remaining hookwire were recovered by additional resection.

Other complications have included minor pneumothorax (7.5%~40%), lung parenchyma hemorrhage (13.9%~36%), and subcutaneous emphysema (5%). A large amount of hemothorax and massive air embolism are rarely reported (20-26). Moreover, there are some anatomical locations that would be a limitation for the procedure, including apical localization, diaphragmatic localization, and location near the great vessels. Surgeons should consider other localization techniques for such nodules.

Dye localization

Localization of pulmonary nodules by methylene blue dye injection was first reported 20 years ago (27). The success rate is high, and it has a short localization procedure time. This procedure can be easily performed in most institutes with CT-guided biopsy technical components and equipment without additional costs. There is almost no anatomical limitation compared to that for hookwire localization. Additionally, radiologists and surgeons are not exposed to radiation.

The major disadvantage of this procedure is that the blue dye may rapidly diffuse into the surrounding lung parenchyma. Therefore, the localization procedure requires immediate surgery upon completion. One method using methylene blue-stained autologous blood was reported to avoid rapid dye diffusion (28). Lin *et al.* first reported using patent blue vital dye for localization, and their

results showed high accuracy and safety (29). Other minor complications have included minimal pneumothorax and intrapulmonary hemorrhage. Anaphylaxis to dye is a lethal complication, but it is rarely reported (30).

Microcoil and fiducial marker placement

Unlike localization with a hookwire, no wire is left protruding extracorporeally after CT-guided localization with metallic microcoils and fiducial markers (31-36), and it may decrease the discomfort of patients during the waiting time to enter the operating room. The size of platinum microcoils is about 15–80 mm in length and 4–5 mm in diameter, and the size of gold fiducial markers is 1.2 mm × 3 mm (31-36). The procedure is similar to that for hookwire localization. The microcoil is passed through a coaxial needle and deployed into the lung parenchyma distal to the needle. Compared to direct visualization of the localized site with hookwire and dye localization, this localization technique requires fluoroscopic guidance during the VATS procedure and increases radiation exposure for surgeons. The success rate is 93%~98.4%. Microcoil and fiducial marker migration leads to localization failure and may occur in 3%~10% of patients (31-36). Other complications include air embolism, fiducial marker embolization, focal intrapulmonary hemorrhage, pneumothorax, and hemothorax.

Contrast medium injection

Instead of using metallic materials to localize the lung nodule, some physicians inject a water-insoluble contrast medium, such as barium or lipiodol, within or around the lung nodule for localization (37,38). These contrast media can be injected by CT-guided needle injection or by CT-guided bronchoscopy injection. Then, the labeled nodules can be intraoperatively detected by fluoroscopy. Because barium may be interpreted as a lesion on pathologic examination and also may cause inflammatory changes in the lung parenchyma, using barium localization may influence pathological diagnosis. Therefore, some authors suggest using lipiodol rather than barium (38). Lipiodol can be retained in the lung parenchyma for a long time, up to 3 months after injection. In addition, lipiodol also diffuses to a very small area in the lung parenchyma. Therefore, the patient does not need to hurry to the operating room immediately after localization in the radiology unit. Nodules are easily identified during fluoroscopy, and the reported success rate is 100% (37,38).

As for other CT-guided percutaneous marking procedures, complications include pneumothorax, minimal hemothorax, and air embolism. The contrast medium could also induce embolisms because it is water-insoluble. Therefore, the injection site should be checked to avoid intravascular injection, and the suggested injection amount is <0.5 mL (38).

Radiotracer-guided localization

Radiotracer-guided localization uses gamma-emitting radioisotopes (technetium 99, Tc99m) attached to large albumin molecules for localizing lung nodules with CT-guided needle injection (39-42). Post-procedure scintigraphy is usually performed to confirm the location of the radiotracer. Gamma-ray emissions can be detected intraoperatively by a probe converting them into digital counts as well as audio signals. The area with the strongest signal can be identified as the lesion site. This technique was first reported by Chella and colleagues in 2000 (39). Thirty-nine patients were included, and their results revealed a 100% successful resection rate (39). The radiotracer can remain stable for up to 24 hours. Therefore, surgeons can use the probe continuously to localize lung nodules during the operation. The disadvantage is that this technique is highly facility-dependent due to the radiotracer, gamma probe, and radiation protection equipment. Surgeons and radiologists may be exposed to the radiation. Other complications are the same as those previously described for CT-guided percutaneous marking procedures, including pneumothorax, hemothorax, and focal intrapulmonary hemorrhage.

Dual localization

Most institutes may use a single technique for lung nodule localization. Kang and colleagues reported their experience using dual localization with a hookwire and radiotracer/lipiodol for needlescopic resection of small lung nodules (43,44). The purpose of dual localization is to avoid failure from hookwire dislodgement and to improve the successful resection rate. The time required for their dual localization was 10.8–13.1 minutes, and the success rate was 100%. They demonstrated that the dual-marking technique is safe, accurate, and not time-consuming.

CT-guided localization in a hybrid operation room

Currently, the previously described common localization techniques are primarily performed preoperatively in the radiology unit. Patients feel discomfort because they have

to undergo an invasive procedure with only local anesthesia or with no anesthesia. The subsequent starting time for the operation is often unpredictable. Transportation of patients may also increase the duration from localization to surgery and increase the possibility of complications, such as pneumothorax and hemothorax. Therefore, it is ideal to use a hybrid operating room for the intraoperative assessment and localization of the indeterminate small lung nodule. Another advantage is that even if the first localization failed, a salvage CT scan can be performed and a second localization procedure performed immediately. Intraoperative CT scans can also provide information on the resection margin. Preoperative localization of lung nodules in a hybrid operating room was first reported in 2013 (17). Zhao *et al.* reported their experience of image-guided single-port VATS in a hybrid operating room in 2016 (18). The only concern is the availability of facilities. Most institutes may have only one or two hybrid operating rooms. It is not possible to perform VATS lung resection for all patients with indeterminate lung nodules in only one hybrid operating room. Therefore, the hybrid operating room should be reserved for difficult cases.

Bronchoscopic-guided techniques—electromagnetic navigation bronchoscopy

Flexible bronchoscopy is limited in that it is unable to guide instruments directly to peripheral lesions. Therefore, electromagnetic navigation bronchoscopy (ENB) with a steerable instrument has been proposed and its feasibility approved for the biopsy of peripheral lung nodules for one decade (45-47). The ENB bronchoscope consists of four components, including a sensor probe with a steering mechanism that is able to navigate the bronchial tree, an extended working channel that can carry either the sensor probe or a flexible instrument, an electromagnetic location board, and computer software that converts thin-cut CT scans into images with three-dimensional virtual bronchoscopy reconstruction and a planned navigation route (45). It enables real-time navigation to the peripheral lung nodules that are invisible on flexible bronchoscopy and subsequent biopsy through the working channel.

Anantham and colleagues reported their early experience using ENB-guided fiducial marker placement for Cyberknife radiosurgery of lung tumors (48). They demonstrated the safety and accuracy of this technique. The fiducial markers were successfully deployed in eight of nine patients. Recently, ENB was used for intraoperative localization of lung tumors (49,50). The entire procedure and surgery is performed in the operating room. The localization procedure is performed under general anesthesia. Therefore, patients do not experience discomfort associated with these invasive preoperative procedures.

ENB-guided dye localization has been proven to be a safe and effective technique (49). Anayama and colleagues reported an animal study that used ENB and a near-infrared fluorescence thoracoscope for the resection of lung nodules (50). They showed the possibility of this technique to localize multiple lung nodules. ENB can precisely localize peripheral lung lesions in the general operating room without the requirement of a CT scan system, which is required for a hybrid operating room. The ENB localization procedure is performed just before surgery begins. Therefore, the common complications of pneumothorax and hemothorax are not of concern.

Other techniques

Intraoperative ultrasonography

The use of thoracoscopic ultrasonography for the localization of lung nodules has been reported since the beginning of thoracoscopic surgery in the 1990s (51-57). The thoracoscopic ultrasound probes are usually 10 mm in diameter and are either rigid or flexible. In a completely deflated lung, the lung nodule can be identified as a hyperechoic lesion with a hypoechoic shadow beneath the nodule (57). This technique can be applied to any pleural surface in the thoracic cavity. Small hard nodules can be easily identified. Although ground-glass nodules are more difficult to localize using this method, Kondo *et al.* demonstrated that intraoperative ultrasonography performed by experienced sonography specialists can both safely and effectively localize ground-glass nodules in a completely deflated lung (57). However, the procedure is highly operator-dependent and can only be used successfully by experienced ultrasonography specialists. Additionally, localization using intraoperative ultrasonography requires complete collapse of the lung, which is often not possible in patients with emphysema. These disadvantages may limit the use of intraoperative ultrasonographic localization in current minimally invasive thoracoscopic surgery.

Intraoperative near-infrared imaging

Recently, Keating *et al.* reported a novel technique of using intraoperative near-infrared imaging (NIR) to identify

lung cancer (58). The patient received indocyanine green injection 4 hours before surgery. Using NIR imaging during VATS, the surgeon could detect the invisible and impalpable nodules and resect them with a negative margin. It provided real-time information to the surgeons during the operation. The disadvantages may include false-positive and negative fluorescence, as well as limitations regarding tissue penetration. This novel technique may improve oncologic outcomes by facilitating early intraoperative detection of small, invisible multiple lung malignancies.

Conclusions

Each localization method has its advantages and disadvantages. It may not be possible to establish a gold standard for localizing indeterminate lung nodules since there is lack of comparative clinical trials. In addition, physicians may also choose different techniques in different institutes based on the limitations of their facilities. The key point is for surgeons to understand the advantages and disadvantages of each technique, and to select the appropriate one for different patients with different tumor locations. The use of a hybrid operating room for intraoperative localization of indeterminate lung nodules could avoid patient transport, reduce patient discomfort, and may become a trend in the future.

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Footnote

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Management strategy of solitary pulmonary nodules

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Abstract: Solitary pulmonary nodules (SPNs) are increasingly detected with the widespread use of chest computed tomography (CT) scans. The management of patients with SPN should begin with estimating the probability of cancer from the patient's clinical risk factors and CT characteristics. The decision-making process need to incorporate the probability of cancer, the potential benefits and harms of surgery, the accuracy of the available diagnostic tests and patient preferences. For patients with a very low probability of cancer, careful observation with serial CT is warranted. For patients in the intermediate range of probabilities, either CT-guided fine-needle aspiration biopsy (FNAB) or positron emission tomography (PET), is recommended. For those with a high probability of cancer, surgical diagnosis is warranted.

Keywords: Solitary pulmonary nodule (SPNs); ground-glass opacity (GGO); subcentimeter nodules; management strategy

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Lung cancer is currently the leading cause of cancer deaths worldwide (1). Clinically, most patients are diagnosed at an advanced stage, with only about 15% have the opportunity of surgical resection. Early detection followed by surgical resection of stage I lung cancer may lead to a 5-year survival rate of 54%~73%, while those with stage IV diseases have a 5-year survival rate of only 2% (2,3). With the established role of low-dose helical computed tomography (CT) screening for lung cancer (4-6), and the wide application of high-resolution CT, solitary pulmonary nodules (SPNs) are increasingly detected (7). Accurate assessment, proper treatment and timely surgical resection of malignant pulmonary nodules will be highly beneficial to the survival of patients with lung cancer. By reviewing the latest literature, combined with our experience in the clinical management of SPNs, we summarized the relevant clinical problems and treatment strategies in this review.

Definition of pulmonary nodules

Currently, an accepted definition of SPNs is a single, well-circumscribed, radiographic opacity less than or equal to 30 mm in diameter that is completely surrounded by aerated lung and is not associated with atelectasis, hilar enlargement, or pleural effusion (8,9). SPNs can be caused by a variety of factors, including malignant diseases such as bronchogenic carcinoma, carcinoid tumors, lymphoma and single lung metastases from other tumors, or a range of benign lesions such as non-specific granuloma, specific granulomatous infections and hamartoma (10).

Pulmonary nodules should be characterized on the basis of number, size, and density. In recent years, an important type of pulmonary nodules has gradually increased, namely the sub-centimeter nodules, which refer to those in a diameter less than or equal to 8 mm (11). Studies have shown that sub-centimeter lung nodules have an overall low degree of malignancy (12). With high-resolution CT, lung nodules can be categorized in a more accurate and detailed way. Ground-glass opacity (GGO) is a special type of pulmonary nodules. GGO is a sign of slightly increased density on the high-resolution CT, in which the bronchial and vascular textures are still visible (13). This sign is a characteristic instead of specific imaging finding, which can be found in multiple lesions in the lung (14). Based on the

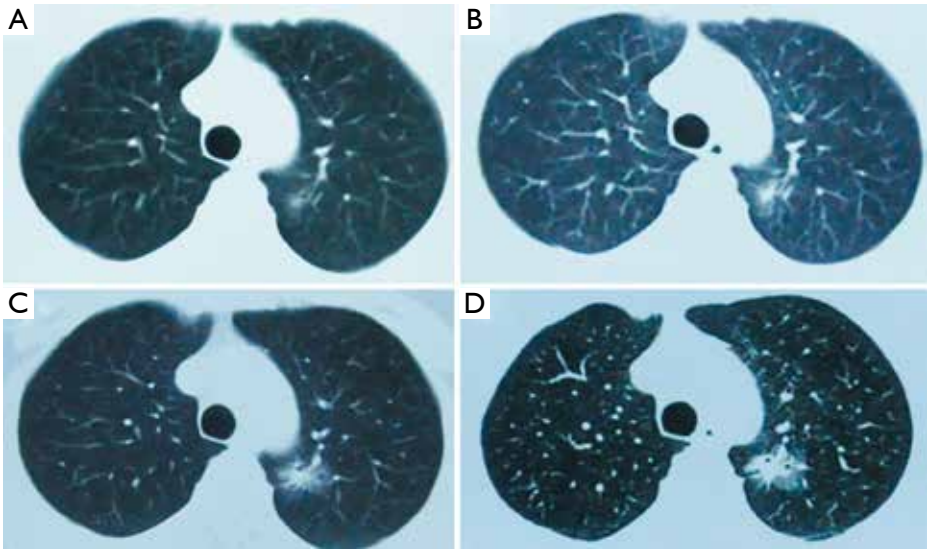

Figure 1 (A) Chest CT scan indicated GGO in the upper left lung, in the size of about 8 mm in April 2006; (B) In January 2008, the chest CT scan found GGO in the upper left lung in a slightly increased size of about 10 mm, with central consolidation; (C) In June 2011, the chest CT showed significant enlargement of the GGO lesion in the upper left lung to about 16 mm; (D) In October 2012, the chest CT scan lesions showed significant enlargement to about 24 mm, with increased central consolidation and burr changes around the lesion. Abbreviation: CT, computed tomography; GGO, ground-glass opacity.

presence of solid tissue component on high-resolution CT, GGO can be classified into three types: pure GGO (pGGO), mixed GGO (mGGO) and solid nodules (15).

In clinical settings, we often encounter patients with GGO, and delayed diagnosis is common due to suboptimal follow-up visits. A 47-year-old female patient without history of smoking was diagnosed with right tuberculous pleurisy in our clinical center in 2002. Following anti-tuberculosis treatment, the patient came to our tuberculosis clinic for follow-up visits every 2-3 years. In April 2006, the chest CT scan indicated GGO in the left upper lung, in the size of about 8 mm (*Figure 1A*). At the follow-up visit in January 2008, the chest CT scan found GGO in the same location in a slightly increased size of about 10 mm, with central consolidation (*Figure 1B*). In June 2011, another follow-up CT showed significant enlargement of the GGO lesion in the left upper lung to about 16 mm (*Figure 1C*). However, in October 2012, the chest CT scan lesions showed significant enlargement to about 24 mm, with increased central consolidation and burr changes around the lesion (*Figure 1D*). A positron emission tomography (PET)/CT scan indicated a SUV of 1.7 of the left upper lung lesion. Surgery was performed to remove the lesion directly, and postoperative pathology indicated adenocarcinoma at stage IA.

Assessment of the probability of malignancy for pulmonary nodules

The probability of malignancy varies depending on the size of pulmonary nodules. Lesions larger than 30 mm in diameter are defined as masses instead of nodules. Resent study results have shown that masses are more likely suggestive of malignancy (15). In many lung cancer screening trials, the probability of malignancy is 0%~1% among pulmonary nodules smaller than 5 mm in diameter, 33%~64% in those from 11 to 20 mm in diameter, and up to 64%~82% in nodules larger than 20 mm (16). The boundary of nodules is also helpful in evaluating the malignancy. In general, irregular, lobulated or burr-like boundaries are more likely to be malignant, compared with a smooth margin (16). Compared with solid nodules, ground-glass opacities or semi-solid pulmonary nodules are more likely malignant (17).

Evaluation and determination the probability of malignancy for pulmonary nodules is essential to the subsequent management and treatment. First of all, an assessment of the probability should be conducted based on a patient's clinical risk factors and characteristics of the pulmonary nodules on CT images (10). The clinical evaluation includes a review of medical history and

Table 1 Risk factors for lung cancer and risk of malignancy in patients with pulmonary nodules

Factors	Tumor risk		
	Low	Middle	High
Size of pulmonary nodules (mm, in diameter)	<8	8-20	>20
Age (years)	<45	45-60	>60
Tumor history	Without tumor history		With tumor history
Smoking history	Never	Smoking, <1 pack per day	Smoking, ≥1 pack per day
History of smoking cessation	Having quit smoking for ≥7 years	Having quit smoking for <7 years	Never quite smoking
Chronic obstructive pulmonary disease	No	Yes	
History of asbestos exposure	No		Yes
Nodule characteristics	Smooth	Lobulated	Burr-like

Table 2 CT scanning frequency of subcentimeter nodules (<8 mm)

Nodule size	Without risk factors for lung cancer	With risk factors for lung cancer
≤4 mm	Selective follow-up	First follow-up within 12 months, and no further follow-up is required if the condition is stable
>4-6 mm	First follow-up within 12 months, and no further follow-up is required if the condition is stable	First follow-up within 6-12 months, and a further follow-up should be arranged within 18-24 months if the condition is stable
>6-8 mm	First follow-up within 6-12 months, and a further follow-up should be arranged within 18-24 months if the condition is stable	First follow-up within 3-6 months, and the second follow-up within 9-12 months; and a further follow-up should be arranged within 24 months if the condition is stable
>8 mm	Follow-up visits should be arranged at months 3, 9, and 24, with dynamic contrast-enhanced CT, PET and/or biopsy	Same as patients without the risk factors

Abbreviations: CT, computed tomography; PET, positron emission tomography.

examination of symptoms. High probability of malignancy is correlated with such clinical risk factors as the nodule size, age, history of cancer, smoking history, history of chronic obstructive pulmonary disease, and history of asbestos exposure. At present, the most accepted criteria is the evaluation criteria for probability of malignant in pulmonary nodules put forward by Ost *et al.* see *Table 1* (8,12,14).

Management of solitary pulmonary nodules (SPNs)

Basic management for patients with pulmonary nodules includes three steps: (I) continuous CT scans for close follow-up observation; (II) further diagnostic tests (imaging, biopsy, or a combination of both); and (III) surgical resection. Obviously, if the probability of malignancy is 0, careful follow-up observation will be the optimal choice. Conversely, if the probability is close to 1, surgical resection following an appropriate staging will be the most appropriate option. For those with a malignant probability between 0 and 1, further examination is the best choice (16). These three steps will be elaborated as below, with emphasis on the timing, supporting signs and limitations, as well as the uncertainty.

Careful follow-up observation

This mainly refers to the continuous monitoring of CT scans, usually applied for patients with a relatively low probability of malignancy before the test (<5%~10%) (10). Many lung cancer screening trail results show that careful follow-up observation is an optimal treatment strategy as screening is often used among those with pulmonary nodules that have a relatively low probability of malignancy (18,19). This strategy is mainly limited by the uncertainty in which a risk of delayed diagnosis is possible, especially when metastases are likely to occur during the observation period, which could have been prevented by early surgical resection. Although the optimal imaging technique is yet to be identified, Fleischner Society has recommended a consensus on the follow-up timing for lung nodules, mainly based on nodule size and presence or absence of risk factors for lung cancer (20,21). The details are shown in *Table 2* (22).

Most malignant lesions have a growth doubling time of 20-300 days. Therefore, clinicians tend to accept that stable imaging results for two years are indicative of benign lesions (23,24). Some studies have shown that pGGO, semi-solid lesions and solid lesions have an average doubling time of 813, 457, and 149 days, respectively (25). Thus, some investigators suggest that once pGGO nodules are found, otherwise healthy patients should receive follow-up imaging visits for more than two years. Despite the above shortcomings, stable imaging findings for two years are still considered an important basis for differentiating between benign and malignant nodules. For certain patients with GGO or semi-solid nodules, the follow-up period can be properly extended. Growth acceleration or generation of solid components confirmed by continuous CT scans will warrant further histological diagnosis, often via CT-guided needle biopsy or surgery (8).

Diagnostic testing

When the probability of malignant nodules is at the moderate level of around 10%~60%, further diagnostic testing is the recommended strategy. These may include PET/CT, CT-guided needle biopsy and bronchoscopy.

PET

Studies have shown that the sensitivity and specificity of PET for the diagnosis of malignant lesions can reach 87% and 83%, respectively (20). When the pre-test probability of malignancy is low and PET results are negative, careful follow-up observation can be considered. However, PET also has its shortcomings. Firstly, PET is not sensitive for nodules smaller than 8-10 mm in diameter (26). For patients with *in situ* adenocarcinoma, carcinoids and mucinous adenocarcinoma, PET may provide a false negative result, and false positive findings may occur in patients who have inflammatory reactions (sarcoidosis or rheumatoid nodules) or in a status of infection (fungal or mycobacterial infections).

CT-guided fine-needle aspiration biopsy (FNAB)

FNAB is a common method for lung tissue biopsies in clinical settings, particularly for SPNs located close to the chest wall. The diagnostic accuracy mainly depends on an operator's positioning and puncturing skills, in addition to the pathology technical level that may have a certain impact on the results.

Fiber optic bronchoscopy (FOB)

FOB-based pathological techniques for the diagnosis of SPNs include bronchial brush cytology (BB), bronchial alveolar lavage (BAL) and transbronchial lung biopsy (TBLB). The development of endobronchial ultrasound, ultrathin bronchoscopy and electromagnetic navigation has improved the sensitivity of TBLB.

Surgery

In the case of a high probability of malignant pulmonary nodules (>60%~70%), video-assisted thoracoscopic surgery (VATS) is the recommended strategy, for it satisfies the needs of both diagnosis and further treatment. With a benign result from intraoperative frozen pathology, only wedge resection will be needed. For malignant pathological findings, surgical resection should be selected in combination with systematic lymph node dissection.

Clinical pathway for management of pulmonary nodules

The treatment strategy for pulmonary nodules should be developed taking into account the probability of malignancy, risk of surgery, difficulty of diagnostic testing and individual preference of patients. The decision-making process should begin from a review of the medical history and physical examination, for the purpose of assessing the tumor probability and risk of surgery. We have developed a new strategy flowchart for the management of SNPs based on the specific strategies in 2013 ACCP guidelines for lung cancer diagnosis and treatment (27), in combination with the clinical experience presented by Ost (10). The strategy for solid pulmonary nodules is depicted in *Figure 2*. In view of the slow growth rate of GGO nodules, specific treatment is required for such GGO or semi-solid lesions. We recommend follow-up examinations shortly after a patient visit, followed by diagnostic puncture or surgical resection to yield a pathological diagnosis as soon as possible. The process is detailed in *Figure 3*.

To sum up, the diagnosis and treatment of pulmonary nodules should start from assessing the probability of malignancy, and in turn evaluating the pros and cons of surgery as well as the consequences of treatment, while taking into account a patient's physical condition, complications, and personal preference. Surgery is preferred for patients with a high probability of malignancy. For those with a moderate malignant probability, CT-guided needle

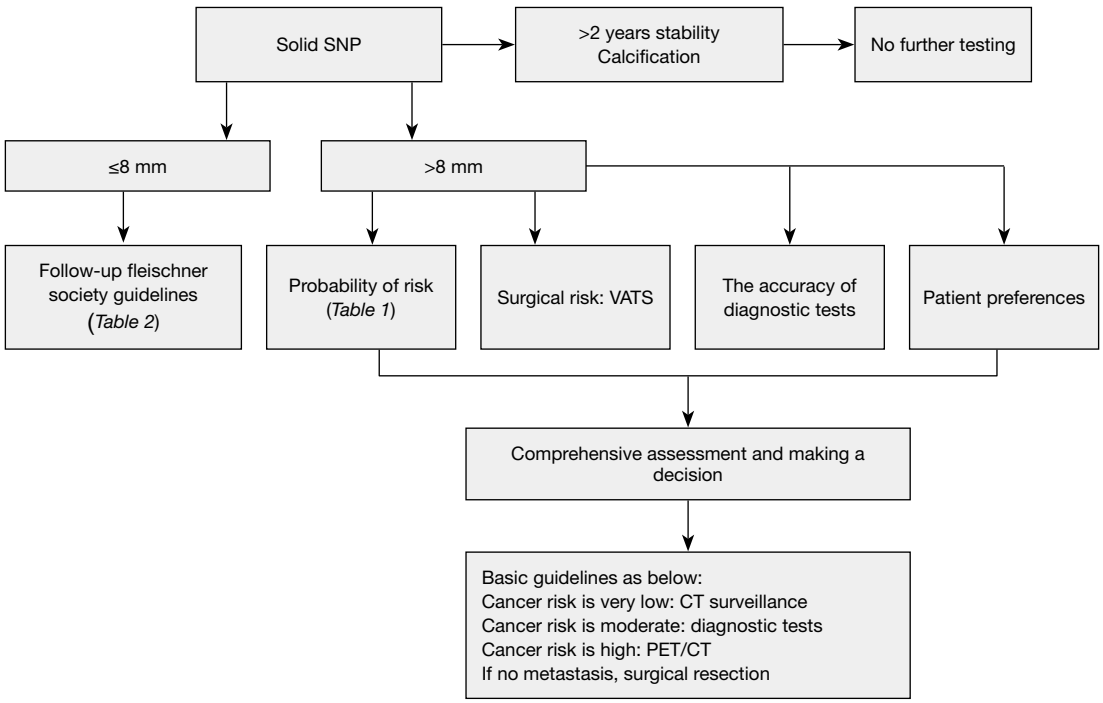

Figure 2 Flowchart for managing solid pulmonary nodules.

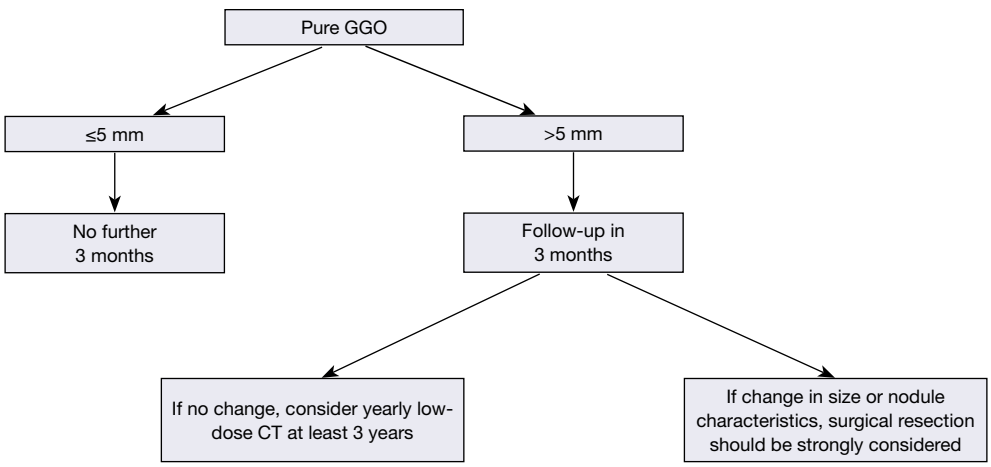

Figure 3. Flowchart for managing pure GGO nodules. Abbreviation: GGO, ground-glass opacity.

biopsy or PET scans will be the best choice.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Preoperative CT-Guided percutaneous wire localization of ground glass pulmonary nodules with a modified Kopans wire

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Purpose: To report a technique of using a modified Kopans wire to localize ground glass pulmonary nodules prior to resection.

Methods: CT-guided preoperative localization of ground glass nodules was performed using the modified Kopans wire.

Results: In both cases, the wire successfully localized the ground glass nodule and the surgeon was able to remove the nodule during video-assisted thoracoscopic wedge resection.

Conclusions: Preoperative CT-guided insertion of the modified Kopans wire can result in successful wedge resection of ground glass nodules. The reinforced segment of the modified Kopans wire serves as an excellent source of palpation and localization for the surgeon.

Keywords: CT-guided; modified Kopans wire; ground glass nodules

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Introduction

Preoperative localization of breast lesions with a hookwire has become a standard radiologic practice (1-3). The technique is advantageous because the needle is accurately positioned under image guidance and once deployed, the hook maintains the wire in position until the patient can undergo surgical resection of the suspicious lesion (4). With the advent of video-assisted thoracoscopic surgery (VATS), thoracotomy is no longer required for the excision of peripheral lung nodules. However, VATS is limited to lesions which can be seen or palpated by the surgeon. Failure to visualize or palpate a lesion can lead to conversion thoracotomy rates of up to 46% (5). Preoperative localization of lung nodules which are too small to palpate or too far from the pleural surface to see or palpate during thoracoscopy was first described by Mack *et al.* (6).

This technique involves placement of a wire in or adjacent to a pulmonary nodule using CT guidance. Currently there are no localizing wires available specifically designed for lung tissue. Previous reports of localization have described the use of the nonmodified Kopans, Hawkins, and other innovative wires in localizing solitary pulmonary nodules (7-9). The majority of cases of wire localization have involved solid pulmonary nodules. We present two cases of preoperative localization of ground glass nodules (GGNs) using a modified Kopans wire. The modified Kopans differs from the nonmodified in that it bears a thick reinforced segment which is designed to be in or adjacent to the lesion. This reinforced segment allows for better palpation and visualization. To our knowledge, this is the first publication describing localization with this form of wire and specifically for GGNs.

Case 1

A 46-year-old woman underwent a CT chest for evaluation of chronic cough. The CT demonstrated a 1cm GGN

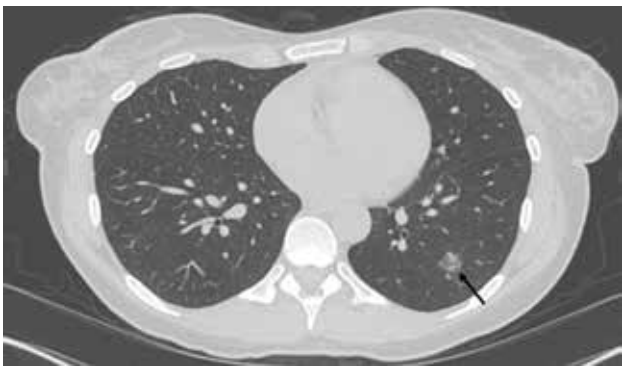

Figure 1 Supine transaxial CT chest image demonstrates 1 cm ground glass nodule in the central portion of the left lower lobe (arrow).

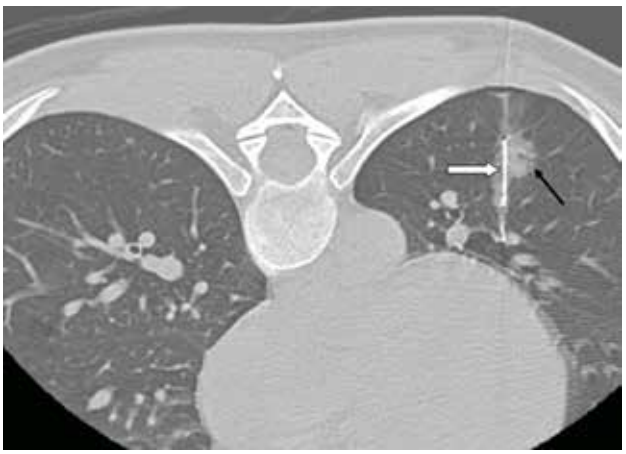

Figure 2 Prone transaxial CT chest image after placement demonstrates the hookwire (white arrow) adjacent to the ground glass nodule (black arrow). Note the positioning of the reinforced portion of the wire is adjacent to the ground glass opacification.

in the central portion of the left lower lobe (*Figure 1*). This nodule was later biopsied and the final pathology documented atypical cells suspicious for adenocarcioma *in situ* (formerly known as bronchioalveolar carcinoma). Surgical resection through VATS was planned but because of the ground glass nature of the nodule and its distance from the pleural surface, preoperative wire localization was requested.

The wire localization was performed using a helical CT scanner (HiSpeed Advantage; General Electric Medical Systems, Milwaukee, WI). The optimal skin entry was determined following consultation with the referring surgeon. Conscious sedation was performed using a combination of Fentanyl and Versed. Following informed consent, the patient was positioned prone on the CT scanner table. An initial scan with 2.5 mm sections through the area of the suspected nodule was performed so that the entry skin site, depth, and angulation of the needle could be planned. The skin entry site was marked and prepped with chlorhexidine and draped in the usual sterile fashion. The length of the hookwire (Modified Kopans; Cook, Bloomington, IN) was determined by the depth required to reach the lesion from the skin surface plus an additional 1.5 cm in order to position the stiff portion of wire adjacent to or within the nodule. Following local anesthesia of the soft tissues with 1% lidocaine, using serial CT scans to confirm locations, a 20-gauge spinal needle was positioned adjacent to the nodule. Once the tip was placed at the desired location, the stylet was removed and the hookwire was deployed by pulling back the spinal needle; additional CT image confirmed final placement (*Figure 2*). The portion of wire external to the patient was secured to the patient's skin in a sterile fashion with gauze and tape. The patient was then transferred to the operating room for wedge resection. A small pneumothorax was present at the completion of the procedure. The patient underwent successful wedge resection of the nodule and the localizing hookwire. Final pathology of the nodule confirmed adenocarcioma *in situ*.

Case 2

A 71-year-old male who underwent a CT abdomen and pelvis in June 2010 for work up of additional treatments for his Crohn's disease, was found to have a 1.5 cm GGN in the right lower lobe (*Figure 3*). He had a 6-month follow up PET/CT which demonstrated slight interval increase in size of the nodule without discernable hypermatebolism beyond background. The patient reported no respiratory symptoms. This nodule was suspicious for adenocarcinoma *in situ* based on its imaging characteristics and surgical resection was planned. Due to the ground glass nature of the nodule, preoperative wire localization was requested.

The procedure was performed with a similar technique to case 1. Following local anesthesia of the soft tissues with 1% lidocaine, using serial CT images for guidance, a 20-gauge spinal needle was advanced into the nodule. Once the tip was placed at the desired location, the stylet was removed and the hookwire was deployed by pulling back the Chiba needle; additional CT images confirmed placement (*Figure 4*). The portion of the wire external to the patient

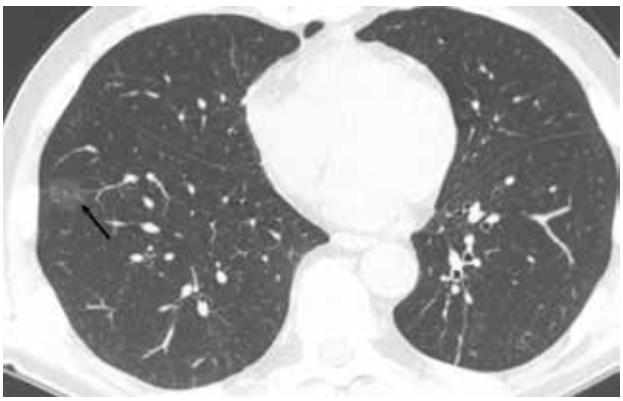

Figure 3 Supine transaxial CT chest image demonstrates 1.5 cm ground glass nodule in the peripheral right lower lobe (arrow).

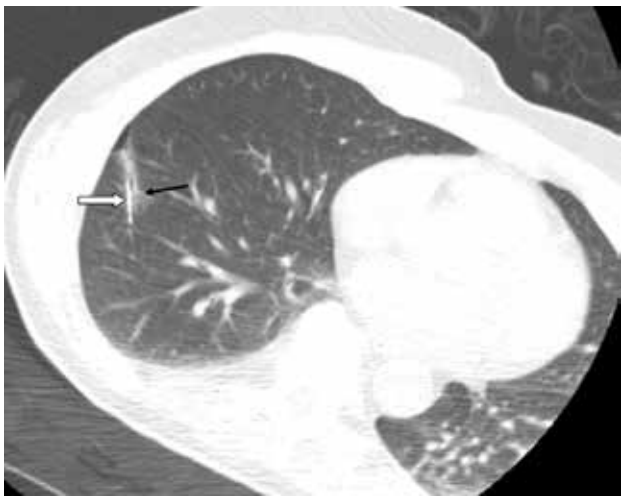

Figure 4 Left lateral decubitus transaxial CT chest image demonstrates placement of the hookwire (white arrow) adjacent to the ground glass nodule (black arrow). Note the precise positioning of the stiff portion of the wire adjacent to the ground glass opacification.

was secure to the patient's skin in a sterile fashion with gauze and tape. The patient was then transferred to the operating room for wedge resection. A small pneumothorax was present at the completion of the procedure. The patient underwent successful wedge resection of the nodule and the localizing hookwire. Final pathology of the nodule was adenocarcinoma *in situ*.

Discussion

VATS is a minimally invasive surgical solution for resection of solitary pulmonary nodules. However, VATS-assisted wedge resection can be challenging in cases where the nodule is too small or too far from the pleural surface, or lacks sufficient density such as GGNs to be palpable by the surgeon.

Several preoperative and intraoperative nodule localization techniques have been reported in the literature. CT-guided methylene blue or colored collagen injection has been described though is limited by the rapid spread of the dye through the lung parenchyma (10,11).

Intraoperative tattooing of lung lesions has also been described, though this technique requires palpation of the lesion, much like resection without pre-operative localization (12). Intraoperative endoscopic ultrasound has also been used to identify peripheral nodules, but with a high false negative rate up to 40% (13).

Hookwire needle localization of pulmonary nodules was first described by Mack *et al.* (6), using the principles and techniques used for years to locate breast lesions prior to surgery. Several reports have described modifications to this technique. Plunkett *et al.* (14) described the use of the Hawkins III breast lesion localization system (Angiotech Pharmaceuticals Inc; Vancouver, BC, Canada), though wire dislodgement occurred in 2 of 20 patients. Surgical time was prolonged in these two cases, but without having to convert to open thoracotomy.

Shah *et al.* (7) used the nonmodified Kopans wire to localize seventeen nodules in fourteen patients. Only 1 case of wire dislodgement was reported; local pulmonary hemorrhage was detected on post-localization CT in six patients. All nodules were successfully resected. Shepard *et al.* (15) also used the nonmodified Kopans wire; dislodgement occurred in 2 of 10 patients and small pneumothoraces occurred in three patients. Successful nodule resection was performed in all ten patients through VATS.

There is no commercially available hookwire specifically designed for localizing lung nodules. Additionally, there is no consensus with regards to which wire to use for cases of GGNs. We favor the use of the modified Kopans wires; the reinforced segment of the wire allows for an additional tool in visualizing or palpating the nodule. We prefer to deploy the wire through either a spinal needle which bears a stylet. The stylet protects against introduction of air into the pleural space. Once in proper position, the stylet can be quickly removed and the hookwire can be deployed.

Previous reports describe wire localization of solid

pulmonary nodules, with only a few reported cases of GGNs. We believe GGN smay be localized with the same ease, and indeed may become a more common indication for localization given GGNs often lack the density to be easily palpated.

Both our patients experienced a small pneumothorax following wire deployment. This did not affect the patient's status, and were ultimately inconsequential as the patients went immediately to the operating room to undergo VATS. According to the literature asymptomatic pneumothorax may occur in 30% of the patients (16). Additional complications include parenchymal hemorrhages which rarely affect the outcome of the procedure, and potential wire dislodgement following placement. The latter is of particular concern because if the procedure is not salvaged through wide excision, conversion to open thoracotomy may be required.

In both of our cases, the wires successfully localized the lesion for the surgeon and were removed in the operating room. This may be due to the use of the modified Kopans wire, which has a sturdier portion proximal to the hook. In addition, the distance between the hookwire tip and the pleura was always greater than 3 cm, a factor demonstrated to correlate with successful wire localization (16).

In summary, we have described preoperative wire localization of GGNs with a modified Kopans wire resulting in successful surgical resection. The modified Kopans wire, secondary to its reinforced segment is an excellent and effective tool in facilitating thoracoscopic surgery for wedge resection of pulmonary nodules that are too small, too far from the pleural surface, or not dense enough to see or palpate. However, further research is required to determine the optimal pulmonary nodule pre-resection localization technique.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Post-therapeutic positron emission tomography/computed tomography for early detection of non-small cell lung cancer recurrence

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Abstract: Patients after curative treatment of non-small cell lung cancer (NSCLC) have a high risk of loco-regional and/or distant tumor recurrence, especially within the first two years. Timely and accurate detection of recurrence is crucial in order to start salvage or palliative therapies with the overall goal of increasing patients' survival and quality of life. However, with the emerging use of non-surgical curative-intended therapies, follow-up of patients becomes even more challenging, as local recurrence has to be distinguished from various post-therapeutic changes at the site of the primary cancer. Integrated positron emission tomography/computed tomography (PET/CT), which is already an established imaging modality in the staging of NSCLC, is increasingly used in recurrence surveillance algorithms. By detailed morphological information being combined with additional information about the metabolic activity of suspicious sites, determination of suspicious lesions as benign or malignant can be improved. This article reviews the value of integrated PET/CT in assessing recurrence in NSCLC patients after potentially curative surgery and after curative-intended non-surgical therapies and raises as well the issue of cost-effectiveness of PET/CT for follow-up.

KeyWords: Integrated positron emission tomography/computed tomography (PET/CT); non-small cell lung cancer (NSCLC); recurrence; follow-up

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Introduction

Lung cancer comprises almost 25% of the total cancer deaths worldwide (1). Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers (2).

Although surgical resection remains the optimal treatment for early stage NSCLC, approximately 40% of patients with stage I and 60% of patients with stage II NSCLC relapse and die within 5 years after curative resection (3).

Timely and accurate detection of recurrence in patients with NSCLC plays a crucial role with regard to the initiation of salvage therapies with the overall goal of increasing survival.

Positron emission tomography (PET) has shown superior sensitivity and specificity in detecting NSCLC lymph node metastasis compared to standard CT alone (4). PET scans have widely replaced bone scintigraphy for detection of bone metastasis and PET is superior to all other clinically available imaging techniques for the detection of distant metastasis, except for cerebral metastasis (5).

The implementation of integrated positron emission tomography/computed tomography (PET/CT) systems, matching detailed morphological information of CT and

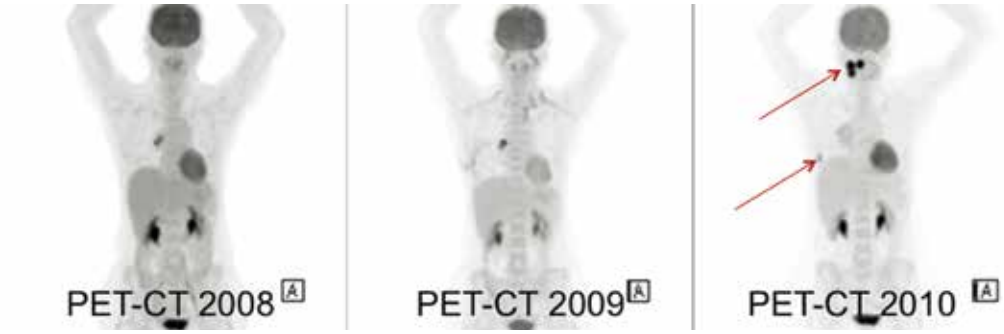

Figure 1 57-year-old asymptomatic patient that underwent annual PET/CT examinations for surveillance of recurrence. Between 2008 and 2009 PET/CT demonstrated stable disease with stable right hilar lymph node metastasis. One year later, PET/CT diagnosed loco-regional recurrence within the right lower lobe as well as distant lymph node metastasis.

metabolic information of structures provided by PET, has further improved accuracy compared to PET or CT alone and has therefore already become an integral imaging modality for diagnosis, staging and response assessment in NSCLC patients (6-9). PET/CT is now emerging as a follow-up imaging modality in these patients. In a study in 2004, reported overall sensitivities, specificities and positive and negative predictive values of integrated PET/CT for diagnosis of NSCLC recurrence were 96%, 82%, 89% and 93%, respectively, compared to 96%, 53%, 75% and 90%, respectively, for PET alone in patients with suspected recurrence who had previously undergone surgical therapy, surgery combined with chemo- or radiotherapy or combined chemo-radiotherapy alone (10).

This review focuses on the value of integrated PET/CT as a state-of-the-art technique in the detection of recurrence of NSCLC after curative surgery, (chemo-) radiotherapy as well as radiofrequency ablation and discusses the cost-effectiveness of PET/CT for recurrence detection.

NSCLC recurrence patterns

Recurrence of NSCLC may be classified as loco-regional recurrence or distant metastasis (*Figure 1*). Distant metastases are the most common form of NSCLC recurrence. Depending on the stage of disease at primary diagnosis and treatment administered, metastatic recurrence comprises 39% to 65.5% of all recurrences (11). About 30% of NSCLC recurrences are reported to be loco-regional. Loco-regional recurrence is located within the treated hemithorax and usually presents with nodules involving the resection staple line or the area that was treated with radiotherapy or RFA, as well as the bronchial stump, pleura, chest wall and lymph nodes (2).

In addition to recurrences, new primary lung cancer is also reported in 1% to 2% of NSCLC patients per year following initial radical therapy (12).

Technical aspects

Performing an integrated PET/CT scan, CT can either be run as low-dose CT, used predominantly for attenuation correction and solely approximate anatomical mapping, or CT is used for both attenuation correction and diagnostic purposes, being then performed with a standard radiation dose and *i.v.* and oral contrast material (13).

The two main advantages gained with the use of integrated PET/CT are on the one hand detection of lesions initially not seen on CT or PET alone, and on the other hand a more precise allocation of metabolic activity to an anatomic structure resulting in a better characterization of the lesion as benign or malignant (7,14). However, sensitivity of PET is decreased in tumors <1 cm, partly due to respiratory motion which can be reduced by respiratory triggered acquisitions at the expense of longer scan times and lower signal-to-noise-ratio (7). Furthermore, PET sensitivity is decreased in the brain. As the most common tracer used for PET scans is 2-deoxy-2-(18F)fluoro-D-glucose (FDG), a radioactively labeled glucose molecule, and the naturally high avidity of brain parenchyma for glucose leads to the problem that cerebral metastases can be obscured (5).

FDG uptake has been observed to vary between different NSCLC histologies, with adenocarcinomas generally being less FDG-avid than squamous cell carcinomas (15). Thus, detection of recurrence is extremely challenging for adenocarcinoma-in situ, minimally invasive adenocarcinoma and lepidic predominant adenocarcinoma since these tumors are often not FDG-avid and false-negative PET

findings have been reported for bronchioloalveolar carcinoma recurrence in 40% of cases (16).

Iatrogenic causes of focal or diffuse FDG parenchymal uptake include: talc deposits after pleurodesis, percutaneous needle biopsy, mediastinoscopy and FDG microembolism (17).

PET/CT in current follow-up guidelines and in clinical practice

Current recommendations for follow-up imaging after NSCLC treatment are based on the knowledge about the high incidence of recurrence during the first 2 years following therapy. The National Comprehensive Cancer Network (NCCN) guidelines from 2010 suggest for patients at all stages of NSCLC routine history and physical examinations every 4 to 6 months in the first 2 years and then annually (18). In patients treated with curative intent in good performance an additional contrast-enhanced chest CT scan is recommended every 4 to 6 months postoperatively for 2 years, followed by a non-contrast-enhanced chest CT annually thereafter. Routinely screening with chest CT alone should be omitted, because many recurrences are extrathoracic (11). PET or brain magnetic resonance imaging (MRI) is currently not recommended for routine follow-up (18).

Yumuk *et al*. performed a survey and interviewed physicians from 38 centres of 12 different countries on which tests they were performing on asymptomatic patients during their post-treatment follow-up. Contradictory to the guidelines, the most commonly used test was a chest CT scan as well as a CT scan of the abdomen at 3 months post treatment (19). PET/CT and contrast enhanced MRI of the brain were done solely in symptomatic patients. These results suggest that a CT scan at 3 months after the end of radical treatment has become a standard in clinical practice with little high quality evidence.

PET/CT for follow-up after surgery

Lung cancer recurs after surgery in 30% to 75% of patients (20). Differentiation of recurrence from post-surgical changes is challenging with CT alone since many benign conditions, including atelectasis, consolidations, and radiation induced fibrosis, are difficult to distinguish from loco-regional recurrence (2).

PET/CT on the other hand, can yield false-positive results from active inflammation, particularly in the acute post-operative phase (21).

False-positive PET/CT results can be explained by an increase in glycolysis due to macrophage infiltration where inflammation is present, and a subsequently higher glucose demand and FDG uptake. In 2008, a British study retrospectively assessed FDG uptake in post-thoracotomy scars of NSCLC patients (22). Increased uptake was seen in 100% of the cases at 1-3 months, in 92% at 3-12 months, and still in 40% of the studies more than one year after surgery all in patients with no evidence of disease on follow-up. FDG uptake was observed to be diffuse in 67% of cases. Tumor recurrence in the scar was found in three cases, with focally increased uptake at 3-8 months after thoracotomy. The authors concluded that increased FDG uptake in post-thoracotomy scars is mainly diffuse, and decreases in incidence and intensity with time, with 60% of studies showing no scar uptake more than one year after surgery. Focally intense scar uptake was suggested to prompt biopsy for suspected recurrence.

These results contradict the usefulness of early post-surgical follow-up with PET/CT within the first three months, whereas usefulness of PET/CT in follow-up as from three months on is supported by these data.

A large prospective study by Choi *et al.*, published in 2011, further evaluated the usefulness of PET/CT first performed one year after curative surgery (23). 358 patients having undergone complete resection of NSCLC were prospectively followed-up with PET/CT and conventional methods for recurrence of NSCLC at 3-month intervals for 2 years and after this at 6 month intervals for the next 3 years. Conventional methods comprised clinical, biochemical and radiographic assessment. Contrast-enhanced chest CT was done every 6 months whereas PET/CT was performed annually for 5 years after resection. Recurrence occurred in 31% of patients. In half of these patients, recurrence was detected with conventional methods. Concerning the other patients, recurrence was detected with both chest CT and PET/CT in 51% and solely with PET/CT in 37%. However, because PET/CT failed to detect 6 small or hypometabolic recurrent lesions, Choi *et al.* recommended as a screening algorithm annual PET/CT scans in combination with low-dose chest CT.

Besides the question of optimal timing of the first follow-up scan, the controversy whether to screen NSCLC patients after potentially curative treatment regardless of clinically suspected recurrence or whether to perform PET/CT only in symptomatic patients is still debated (*Figure 2*).

In this context, a Japanese study published in 2012 retrospectively evaluated the diagnostic accuracy of routinely

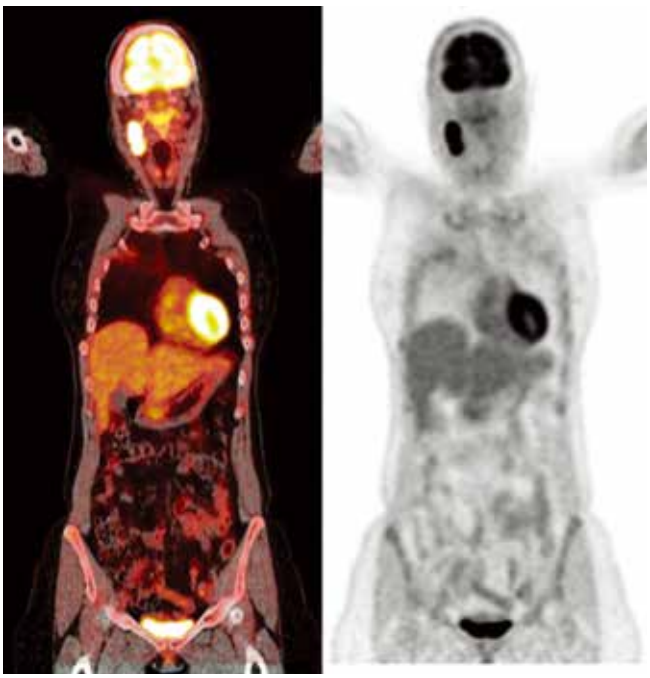

Figure 2 67-year-old asymptomatic patient with cervical metastatic disease that was detected during a follow-up PET/CT examination two years after curative intended chemo-radiation therapy.

performed PET/CT scans in post-operative asymptomatic NSCLC patients without suspicion of recurrence (24). A total of 101 NSCLC patients were followed-up for 5 years with a surveillance algorithm consisting of physical examination, chest radiograph, tumor marker, chest CT, PET/CT and brain MRI. Chest CT and PET/CT were performed in alternation every 6 months for the first 3 years. PET/CT was then performed every 12 months for the next 2 years. A total of 233 studies were acquired. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of PET/CT in recurrence evaluation were 94.4%, 97.6%, 89.5%, 98.8% and 97.0%, respectively. Recurrence rate in this asymptomatic patient cohort was 18%.

Another study with PET/CT in asymptomatic patients being performed at around 1 year after curative resection of NSCLC was conducted by the group of Cho *et al.* (25). The study enrolled 86 patients who had no suspicion of recurrence at the time of the PET/CT scan. 31.4% of the patients had recurrent disease in this cohort and 2 patients had extrathoracic double primary cancer. Six patients had extrathoracic recurrence without intrathoracic recurrence, contradicting the use of chest CT scans alone.

Jimenez-Bonilla *et al.* prospectively evaluated the contribution of PET/CT in patients with all stages of NSCLC with suspicion of recurrence in terms of sensitivity, specificity, impact on therapy and on survival (26). 59 suspicious lesions in 55 patients were investigated. PET/CT showed an overall sensitivity of 100% and 83% specificity. In 27 suspicious lesions where CT results were inconclusive, PET/CT showed 100% sensitivity and 78% specificity. PET/CT had an impact on patients' treatment in 42 of all 59 cases of suspected recurrence. Overall survival of PET/CT diagnosed recurrence at 20 months and 5 years was 44% and 11%, respectively.

In comparison, a large retrospective study from 2009 analyzed post-recurrence survival rates in 123 stage I NSCLC patients who had received curative surgery between 1980 and 2000 (27). Patients either had local recurrence only or both local recurrence and distant metastases. The overall 1 and 2 year post-recurrence survival rates were 48.0% and 18.7%, respectively (27).

Comparing the survival rate observed in the PET/CT study by Jimenez-Bonilla at 20 months (44%) to the survival rate of the Hung study after 2 years (18.7%) especially when further taking into consideration, that Jimenez-Bonilla's group also included patients at more advanced stages of NSCLC and not only stage I patients, these results are very encouraging: The outcome data of the study by Jimenez-Bonilla are suggesting a positive impact on survival using PET/CT for follow-up in the subgroup of symptomatic patients, with the limitation of the small number of patients enrolled.

Besides the high accuracy of PET/CT and its impact on treatment decisions and survival, another interesting issue—also with regard to cost-effectiveness—is the performance of PET/CT in detecting NSCLC recurrence compared to standard radiological examinations: two recent PET/CT studies prospectively enrolled patients that underwent NSCLC resection and assessed the accuracy of whole body PET/CT in recurrence detection in comparison to standard radiological examinations.

Takenaka *et al.* prospectively compared whole-body PET/CT and standard radiological follow-up examinations in the assessment of recurrence in post-operative NSCLC patients (28). A total of 92 consecutive patients with complete resection were enrolled. The standard radiological examination for distant metastasis assessment performed during the initial and the follow-up examinations and for local recurrence after surgery included contrast-enhanced MRI of the brain, contrast-enhanced whole-body CT

and bone scintigraphy. Final diagnosis of recurrence was based on the results of more than 1 year of follow-up and/or pathological examinations. ROC curves were used to compare the diagnostic capability of the two methods for assessment of post-operative recurrence on a per-patient basis. Sensitivity, specificity and accuracy were determined as well. There were no statistically significant differences in the area under the curve of sensitivity, specificity and accuracy between PET/CT and standard radiological examinations (P>0.05). Hence, the authors concluded that PET/CT can be used for assessment of post-operative recurrence in NSCLC patients with an accuracy as good as that of standard radiological examinations; yet, with the non-negligible advantage of only one examination for the patient instead of three. This factor might play a crucial role for an efficient workflow of large departments that follow-up large patient cohorts.

Onishi *et al.* investigated in a prospective study in 2011 the value of qualitative as well as of quantitative PET/CT for the assessment of post-operative intra- and extrathoracic recurrence in NSCLC patients compared to standard radiological examinations (29). 121 patients who had undergone complete resection were followed-up. Again, ROC analysis was used to compare the methods in their assessment of post-operative recurrence on a per-patient basis. Additionally, optimal cut-off values for FDG uptake measurement at a suspicious site detected on the basis of qualitative PET/CT were determined. Analogous to Takenaka's results, areas under the curve for accuracy of qualitative PET/CT and standard radiological examinations showed no significant differences (P>0.05). At an optimal cut-off value of 2.5, specificity and accuracy of combined quantitative and qualitative PET/CT were significantly higher than of qualitative PET/CT and standard radiological examinations alone (P<0.05). Accuracy in the evaluation of post-operative intra- and extrathoracic recurrence in NSCLC patients by qualitative and/or quantitative PET/CT was consequently rated equivalent to or higher than that of standard radiological examinations.

Kanzaki *et al.* retrospectively examined the clinical value of PET/CT in a large cohort of 241 patients with NSCLC after potentially curative surgery and even proposed that conventional imaging for the detection of extrathoracic metastases in patients who underwent potentially curative surgery for NSCLC can be completely omitted (with the exception of brain MRI) if PET/CT performed at least 6 months after surgery is negative, due to its high negative predictive value (30). 490 PET/CT studies were evaluated in this study. PET/CT correctly diagnosed recurrence in 34 of 35 patients and provided true negative findings in 198 of 206 patients who had no evidence of recurrence (sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 97%, 96%, 96%, 81%, and 99%, respectively), indicating a high diagnostic performance in this patient group.

Follow-up of NSCLC after non-surgical treatment

The field of non-surgical therapies of primary lung cancer has grown rapidly in recent years. The use of external beam radiotherapy alone as a curative approach to therapy has been abandoned due to the high local recurrence rate of up to 70% (31). In contrary, minimally invasive image-guided therapies using thermal energies such as radiofrequency ablation, microwave ablation or cryoablation, and as the most common one stereotactic body radiation therapy (SBRT) have emerged as non-surgical treatment options (32). Yet, as the tumor is not resected, surveillance of recurrence and especially of tumor margins is crucial and challenging due to post-interventional parenchymal changes.

PET/CT in NSCLC follow-up after (chemo-) radiotherapy

SBRT has become the standard therapeutic approach for inoperable stage I NSCLC. SBRT induces parenchymal damage leading to fibrosis. It can be difficult to differentiate local recurrence from radiation-induced lung opacity. Radiation-induced fibrosis can appear more than 1 year after the end of therapy (33). Furthermore, secondary radiation-induced pneumonitis has been reported within 9 months after SBRT (32).

A small study by Hoopes *et al.* observed on PET scans in a patient cohort of inoperable stage I NSCLC after SBRT treatment a moderately hypermetabolic activity up to 2 years after SBRT (34). This persistent uptake is being attributed to a more persistent inflammation and fibrosis after SBRT compared to fractionated radiotherapy (7).

Takeda *et al.* retrospectively assessed the additional value of dual-time-point maximum standardized uptake values (SUV_{max}) in PET/CT for detection of local recurrence after SBRT of NSCLC in 214 scans of 154 patients (33). Tri-monthly follow-up CT scans were acquired and PET/CT scans were done one year after SBRT or when recurrence was clinically suspected. On early and late images, optimal SUV_{max} thresholds were identified as 3.2 and 4.2. Using these thresholds, sensitivity and specificity

were 100% and 96%~98%, respectively. The authors therefore stated that SUV_{max} on PET/CT could predict local recurrence after SBRT for localized NSCLC. In a similar study, Zhang *et al.* also investigated whether the additional assessment of SUV_{max} on PET/CT after SBRT could help to predict local recurrence in 128 patients with stage I NSCLC or isolated recurrent/secondary parenchymal NSCLC patients (35). The authors found a SUV_{max} greater than 5, especially more than 6 months after SBRT to be associated with a higher local recurrence rate, whereas SUV_{max} from PET/CT scans performed within 6 months of treatment were not correlated with local recurrence. With the cutoff SUV_{max} of 5, sensitivity for correct prediction of local recurrence was calculated as 100%, specificity was 91%, positive predictive value was 50% and a negative predictive value of 100% was observed. The authors concluded that quantitative PET/CT was helpful for distinguishing SBRT-induced consolidation from local recurrence.

In contrast, van Loon *et al.* hypothesized that early PET/CT scans 3 months after curative-intended (chemo-) radiotherapy could lead to early detection of progressive disease (PD) amenable for radical treatment (36). Therefore, 100 patients with NSCLC were prospectively evaluated. All patients underwent a planned PET/CT scan 3 months after the start of radiotherapy. 24 patients had PD 3 months post-treatment of whom 16 patients were symptomatic. Yet, no curative treatment could be offered to any of these patients, which limits the impact of PET/CT on treatment decisions in the specific population of symptomatic patients. To 3/8 asymptomatic patients who were diagnosed PD, radical treatment could be offered. Progression—according to the EORTC criteria for PET and the RECIST criteria for CT—potentially amenable for radical therapy was in this study solely detected with PET/CT, but not with CT alone (37,38). Thus, van Loon suggested that asymptomatic patients would profit the most from an early PET/CT scan. However, it has still to be proven that the detection and therapy of early recurrence or PD leads to an overall higher survival in this patient cohort.

PET/CT in NSCLC follow-up after radiofrequency ablation (RFA)

Patients with stage I NSCLC who do not undergo surgical treatment are—besides SBRT—predominantly treated with RFA. The most common pattern of recurrence after RFA is loco-regional recurrence (39). As for SRBT, RFA causes focal changes in the lung parenchyma such as ground glass opacities around the treated tumor site (40). So far, there is no consensus existing on a standard protocol for post-RFA follow up. However, after RFA, continuous follow-up imaging seems to be beneficial to the patients because recurrence has been reported to occur throughout the first 2 years post-treatment (39).

Eradat *et al.* proposes an algorithm of CT follow-up 1-2 months after RFA followed by a PET/CT scan at 3 months thereafter alternated by contrast-enhanced CT every 3 months for 2 years (32). Similarly, the group by Beland is proposing contrast-enhanced CT at 3 weeks and 3 months followed by PET/CT at 6 months; alternating CT and PET/CT examinations then performed every 3 months (39).

Cost effectiveness

In spite of the experiences of PET/CT as a helpful staging imaging modality in the treatment of NSCLC and encouraging results concerning the accuracy of PET/CT in detecting recurrence reported in the few follow-up studies performed so far, and mostly enrolling patients with follow-up after surgical therapy, the 2nd edition of the American College of Chest Physicians (ACCP) evidence-based guidelines on the follow-up and surveillance of lung cancer patients did not recommend PET/CT for standard surveillance. The reason given for this decision was a lack of evidence that follow-up PET/CT improves either survival rates or quality of life of NSCLC patients (11).

In the only cost-effectiveness study of NSCLC follow-up so far with 100 patients, van Loon *et al.* prospectively compared long-term cost-effectiveness of 3 different follow-up strategies, all starting 3 months after therapy. The authors either performed a PET/CT scan, a chest CT scan or conventional follow-up with a chest radiograph (41). Cost-effectiveness was expressed in incremental cost-effectiveness ratios (ICERs), calculating the incremental costs per quality adjusted life year (QALY) gained. Both PET/CT- and CT-based follow-up were calculated to be more costly but at the same time also more effective than a chest radiograph follow-up. CT-based follow-up resulted in an incremental cost-effectiveness ratio (ICER) of euro 264.033 per QALY gained compared to a chest radiograph, whereas for PET/CT-based follow-up, the ICER was euro 69.086 per QALY gained. A subgroup analysis of asymptomatic patients undergoing PET/CT resulted in an ICER of euro 42.265 per QALY gained compared to

chest radiograph follow-up. Assuming a ceiling ratio of euro 80.000, PET/CT-based follow-up was calculated to have the highest probability of being cost-effective (73%). The authors therefore concluded that a PET/CT scan 3 months after curative-intended (chemo-) radiotherapy is a potentially cost-effective follow-up method, and is more cost-effective than CT alone. Performing PET/CT scans only in asymptomatic patients seems to be equally effective and even more cost-effective.

Conclusions

Current guidelines do not recommend the use of PET/CT for assessment of NSCLC recurrence. Recommendations of different authors concerning the initiation and frequency of follow-up with PET/CT scans are largely varying between post-surgical NSCLC follow-up and surveillance of patients treated with radiotherapy and radiofrequency ablation. Most studies on NSCLC follow-up were conducted in post-surgical stage I NSCLC patients and PET/CT was mostly performed annually, starting one year after surgical treatment.

Concerning follow-up after non-surgical potentially curative treatment of NSCLC patients, controversial results have been published on the optimal timing of the first PET/CT scans. Different algorithms from different working groups schedule the first PET/CT scan from 3 months on to one year in this patient cohort. Concerning follow-up after RFA, very few studies on follow-up of these patients have been published so far. In two existing follow-up algorithms, PET/CT is performed for the first time 3 months and 6 months after treatment, respectively.

The additional value of quantitative PET measurements in prediction of recurrence has been suggested in the evaluation of thoracotomy scars as well as in the surveillance of patients treated with SBRT.

Despite encouraging results of high accuracy of PET/CT for the assessment of NSCLC recurrence and reports of impact on changes in patient management, controversy exists about whether to follow-up symptom-based or whether to screen on a routinely basis independently of symptoms and clinical findings (10,36).

Currently, PET/CT is rather used in symptomatic patients with suspicion of recurrence. However, impact on therapeutic management was mainly reported for asymptomatic patients with regard to salvage therapies. Nevertheless, high quality evidence is still lacking that intensive surveillance programs and earlier detection of recurrence leads to a survival benefit and despite of one encouraging cost-effectiveness study, incremental costs of integrated PET/CT scanners might probably play a role in decisions for or against surveillance guidelines including PET/CT to come up (41-43).

In the future, large-scale randomized trials should predominantly focus on the impact of PET/CT on treatment outcome. Furthermore, optimal starting point and frequency of follow-up PET/CT scans should be determined, especially in patients treated with the emerging minimally-invasive image-guided therapies and lastly the utility of quantitative PET/CT measurements for recurrence detection has to be clarified.

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Footnote

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Interventional pulmonology approaches in the diagnosis and treatment of early stage non small cell lung cancer

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Abstract: Lung cancer management is complex and requires a multi-disciplinary approach to provide comprehensive care. Interventional pulmonology (IP) is an evolving field that utilizes minimally invasive modalities for the initial diagnosis and staging of suspected lung cancers. Endobronchial ultrasound guided sampling of mediastinal lymph nodes for staging and detection of driver mutations is instrumental for prognosis and treatment of early and later stage lung cancers. Advances in navigational bronchoscopy allow for histological sampling of suspicious peripheral lesions with minimal complication rates, as well as assisting with fiducial marker placements for stereotactic radiation therapy. Furthermore, IP can also offer palliation for inoperable cancers and those with late stage diseases. As the trend towards early lung cancer detection with low dose computed tomography is developing, it is paramount for the pulmonary physician with expertise in lung nodule management, minimally invasive sampling and staging to integrate into the paradigm of multi-specialty care.

KeyWords: Bronchoscopy; gene expression profiling; interdisciplinary communication; TNM staging; radial probe-EBUS (RP-EBUS); virtual bronchoscopic navigation (VBN); electromagnetic navigational bronchoscopy (ENB™)

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Background of interventional pulmonology (IP)

At the dawn of the 20th century, respiratory physicians largely provided medical care in sanatoriums tending to patients infected with tuberculosis. TB was the second leading cause of death in that era behind pneumonias and influenza infections (1,2). Advances in antimicrobials, including isoniazid and penicillin, led to significant improvement in outcomes. During the subsequent decades, tobacco smoking became widespread in the United States. It was not until the mid-20th century that lung cancer was strongly linked to smoking with epidemiological data (3). Since then, pulmonologists have managed the myriad of lung ailments consequent to tobacco addiction, such as emphysema. As lung cancer became the leading cause of cancer deaths in both men and women, the pulmonologist's role in lung cancer care has evolved. Smoking cessation remains the most important role a pulmonologist assumes to prevent lung cancers; as one fifth of U.S. population are smokers, and among the economically disadvantaged, the number increases to about forty percent (4). On the other hand, the management role of pulmonologists in lung cancer has also evolved from diagnosis of late stage lung cancers and risk stratification for surgery, to management of early stage disease with personalized approach in a multidisciplinary setting.

Interventional pulmonology concentrates on the use and development of diagnostic and therapeutic endobronchial techniques (5-7). The IP armatorium consists of (and is not limited to) rigid bronchoscopy, endobronchial laser therapy, electrocautery, cryotherapy brachytherapy and endobronchial or tracheal stent placement and the advanced

Table 1 Current interventional and advanced diagnostic modalities for managing malignant neoplasia of the lung

Diagnostic:
• Endobronchial US
- Radial probe
- EBUS-TBNA
• Narrow band imaging
• Electromagnetic navigation
• Navigational bronchoscopy
• Confocal microendoscopy
Therapeutic:
Extrinsic compression:
• Stent
Intrinsic obstruction:
• Microdebridement
• Rigid bronchoscopy coring
• Argon plasma coagulation (APC)
• Laser (Nd:YAG, CO_2)
• Electrocautery
• Cryotherapy
• Photodynamic therapy (PDT)
• HDR-brachytherapy
Peripheral tumor:
• Fiducial marker placement to assist stereotactic body radiation therapy (SBRT) for inoperable patients with resectable stage I lung CA
• Fiducial marker placement for localization for surgical managament

Abbreviations: EBUS, Endobronchial ultrasound; TBNA, Transbronchial needle aspiration; Nd:YAG, neodymium-doped yttrium aluminum garnet; CO_2, Carbon Dioxide.

diagnostic techniques available to pulmonologists such as endobronchial ultrasound (EBUS) and navigational bronchoscopy (NB) (*Table 1*).

It is important to bear in mind that the field of IP depends on close-working and complementary relationships with the thoracic radiologist, radiation oncologist, and the thoracic surgeon as part of a multidisciplinary team. This review will cover diagnostic and therapeutic techniques that are being used in the management of early stage lung cancer.

Bronchoscopic early detection of malignancy

Lung cancer is the most lethal of solid tumors. Up to 85% are attributed largely to heavy smoking. Furthermore, despite smoking cessation many are still at risk for several years since their last cigarette (8). In the last decade evidence in favor of lung cancer screening with low-dose computed tomography (LDCT) has been shown to be superior to chest X-ray (CXR) (8).

Henscke *et al.* demonstrated in a prospective observational study of 31,567 asymptomatic patients, low dose CT screening resulted in the diagnosis of lung cancer in 484 patients, 85% of whom had Stage I disease, and who after treatment had a 10-year survival rate of 88% (95% CI, 88%~95%) (9). The National Cancer Institute-Sponsored Lung Screening Trial that followed supported its findings. The NSLT was a randomized control trial in which 53,454 patients were randomized to three years of annual low dose CT screening versus plain chest X-ray (8). After three years the NSLT investigators had achieved their primary objective, which was a 20% relative reduction in mortality from lung cancer. The corresponding number needed to screen (NNS) to prevent 1 death after 1 year of screening is 320. Although questions remain about trial design, generalizability, applicability and cost-effectiveness of LDCT in the community, the goal of detecting early stage lung cancer with concomitant reduction in cancer specific mortality has become achievable.

As a result of NLST, the U.S. Preventive Services Task Force has recently updated its original 2004 recommendations regarding lung cancer screening. Its main recommendation, based on the NLST, provides LDCT screening to high risk individuals with at least a 30 pack-year smoking history between the ages of 55-79 years. The prospective efficacy of these recommendations will depend on the ability of the pulmonologist to meet the demands of accurate and timely diagnosis, proper risk stratifications, tissue sampling when appropriate, and familiarity thoracic oncologists' needs beyond tumor types, i.e., molecular profiling.

Early detection of malignancies arising from the central airways by bronchoscopy has also been evaluated over the past decade. Squamous cell carcinomas of the central airways have shown to develop through several stages from metaplasia, dysplasia, carcinoma in-situ (CIS) and advanced invasion (10). The cellular transformation of bronchial carcinomas has been described as a spectrum of lesions from basal layer hyperplasia, metaplasia, dysplasia, and CIS (11).

CIS is characterized by involvement of the entire epithelium with marked cytologic atypia. Bronchoscopic follow-up by autofluorescence bronchoscopy (AFB) and biopsy data among patients with high suspicion for lung cancer either from positive sputum cytology or prior upper respiratory cancers has shown that severe dysplastic lesions were more likely to progress towards CIS and further invasive cancer (12,13). Furthermore, Bota *et al.* showed 75% of CIS lesions, which persisted at 3 months required therapy (13). Currently the American College of Chest Physicians (ACCP) recommendations regarding known CIS and high-grade dysplastic lesions suggest performing follow-up white-light bronchoscopy (WLB) to rule out endobronchial lesions with use of AFB if available (14). However, relatively higher false-positive rates and suboptimal specificity of AFB, likely due to failure to distinguish inflammatory airways from dysplasia, limit its potential to preclude the need for unnecessary biopsies (15).

Narrow band imaging (NBI)

NBI utilizes narrow wavelengths of blue (400-430 & 420-470 nm; B1 & B2, respectively) and green (560-590 nm) light to enhance visualization of abnormal collections of submucosal capillaries (16,17). This strategy has been shown to be highly effective in differentiating normal mucosa from highly vascular precancerous lesions such as angiogenic squamous dysplasia (ASD). ASD is characterized by abnormal collections of microvessels projecting into dysplastic cells within the bronchial mucosa (18). NBI has shown improved sensitivity in detecting ASD not readily seen with WLB or AFB (19-21). Diagnostic yield was similar between NBI and AFB without any increased false-positives suggesting that NBI may serve as an alternative tool in early lung cancer detection. NBI's unique ability to detect early angiogenesis undetectable by AFB with high specificity (85%~90%) and negative predictive value (>90%) has the potential for influencing therapeutic decision-making (22). Currently, the ACCP recommends NBI or AFB, when available, be used to delineate tumor margins in patients who are candidates for early lung cancer resection (23).

Lung cancer diagnosis and staging

The solitary pulmonary nodule (SPN)

The solitary pulmonary nodule, commonly detected incidentally, is among the top reasons for referral to a pulmonologist. Concurrently, as the work on early lung cancer screening evolves, it behooves the pulmonary specialist to become an expert in the management of the solitary lung nodule.

The current ACCP guidelines recommend, depending on patient and SPN features, observation, tissue biopsy and direct surgical excision. The role for pulmonologists for biopsies will be expanding with advancing bronchoscopic techniques. Currently, with more peripheral lesions where tissue biopsy is indicated, the guidelines recommend trans-thoracic needle biopsy (TTNB) as the preferred modality as the diagnostic yield is slightly below 90% (23-25). Traditional transbronchial biopsy with bronchoscopy has a diagnostic yield of only 14%~63% (26). In 2012, Wang *et al.* published a meta-analysis of 39 pooled studies (n=patients >3,000) of all available guided-techniques (discussed below) that demonstrated a pooled diagnostic yield of 70% (25). While this is improved compared to standard bronchoscopy, it still remains below the diagnostic yield of TTNB. Concurrently, Wang reported a pneumothorax rate in TTNB of 25% (15% requiring a chest tube) versus less than 2% (less than 1% requiring a chest tube) in bronchoscopic techniques. The three main techniques used in this field of specialized bronchoscopy are radial probe-EBUS (RP-EBUS), virtual bronchoscopic navigation (VBN) and electromagnetic navigational bronchoscopy (ENB™) (5).

Radial probe EBUS (RP-EBUS)

RP-EBUS uses ultrasound to take samples sequentially. It allows excellent visualization of the bronchial walls and a tumor in situ. It is also the only technology that allows for real-time confirmation that the target lesion has been reached which translates to improved yield over conventional transbronchial biopsy with or without fluoroscopy (27-31). In a prospective cohort study of 131 patients, RP-EBUS demonstrated better sensitivity and accuracy (89% and 100%, respectively) at detecting bronchial wall invasion over CT (75% and 51%, respectively) (32). RP-EBUS uses a flexible bronchoscope to access the bronchiole closest to the nodule, and then a miniaturized radial probe and sheath are passed through the working channel until the nodule is visualized. The probe is removed leaving the sheath in position, then biopsy forceps is inserted through the guide sheath and the nodule sampled (*Figure 1*). Steinfort *et al.* showed in a meta-analysis of 13 studies and 1,090 patients, that RP-EBUS in SPNs

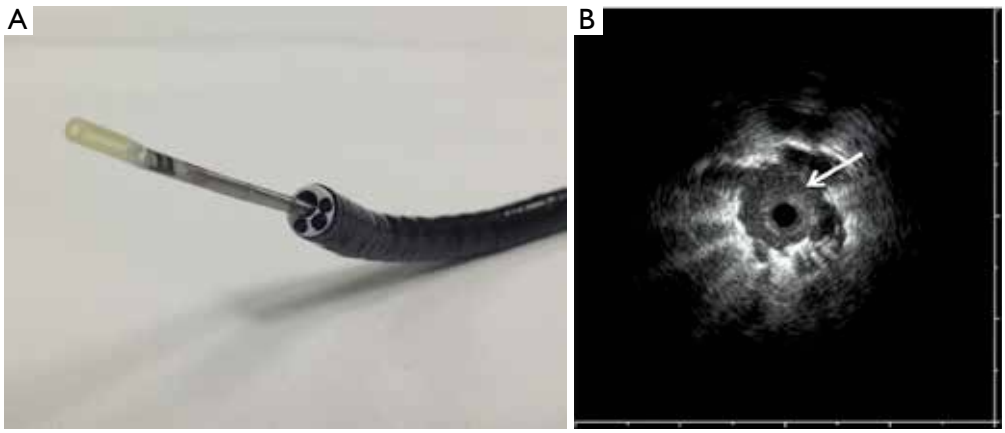

Figure 1 A. Radial Probe 20-mHz Endobronchial Ultrasound fitted into a therapeutic bronchoscopy channel; B. Radial EBUS image of a peripheral lesion (arrow) (Courtesy Olympus Endoscopy USA).

had a point specificity of 1.00 (95% CI, 0.99-1.0) and point sensitivity of 0.73 (95% CI, 0.70-0.76) (33). Eberthardt *et al.* in a randomized control trial showed that RP-EBUS with a guide sheath alone had a diagnostic yield of 69% (34). This increased to 88% when combined with electromagnetic navigational bronchoscopy (ENB™); a diagnostic yield comparable to TTNB and SPNs with a mean diameter of 25 mm.

Electromagnetic navigational bronchoscopy (ENB™)

ENB™ is a technology developed for access to peripheral nodules beyond the reach of conventional bronchoscopes. Akin to global positioning systems (GPS), ENB™ is able to provide real-time orientation of a proprietary sensor probe by utilizing an electromagnetic field generated by a board underneath the patient (16,35). Pre-procedural planning involves importing the patient's CT data and assigning anatomical landmarks including the target lesion. The sensor probe (1 mm diameter × 8 mm long) is loaded into a flexible catheter, and then passed through the working channel of a standard bronchoscope. Guidance is provided by a matched virtual bronchoscopy image aside the real-time video bronchoscopy overlain with pre-determined pathway markers. Once the bronchoscope is wedged into the segment of interest the flexible catheter with the sensor probe is advanced until the target lesion is reached. At this point the sensor probe is retracted leaving the flexible catheter in place to act as an extended working channel (*Figure 2*). The diagnostic yield of ENB™ alone is reported to range from 59%~74% (36-38). While early studies postulated that target lesion size might be significant, recently it is believed that CT-body divergence (a measure of image data registration accuracy) may determine navigational success (36,38). Other factors related to local anatomy and distance influence overall success (39,40). The presence of a bronchus sign significantly improved success to 79% in series of 51 patients by Seijo and colleagues (39).

Recently, a randomized-controlled trial by Asano and colleagues demonstrated virtual bronchoscopy navigational guidance (VBN, a computerized guidance system without electromagnetic correlation) with an ultrathin scope significantly improves diagnostic yield in the right upper lobe, peripheral third and lesions invisible on chest X-ray (41). However, the main limitation of this technique is the lack of real-time confirmation that a nodule has been reached. Addition of radial EBUS has shown to overcome this by increasing diagnostic yield to 88%~93% (42).

Lung cancer staging with convex-EBUS (EBUS-TBNA)

Staging and confirmation of nodal status is central to the diagnosis and management of non-small cell lung cancer (NSCLC) (*Figure 3*). The treatment of choice of stage I and II disease is surgical resection in operable candidates, whereas combined chemo and radiotherapy is indicated for patients with Stage III disease and above (43). In academic settings, a multimodality approach can be considered for functional IIIA patients to undergo surgical resection after neoadjuvant therapy (23). Mediastinal nodal metastases are detected non-invasively with CT and/or positron emission

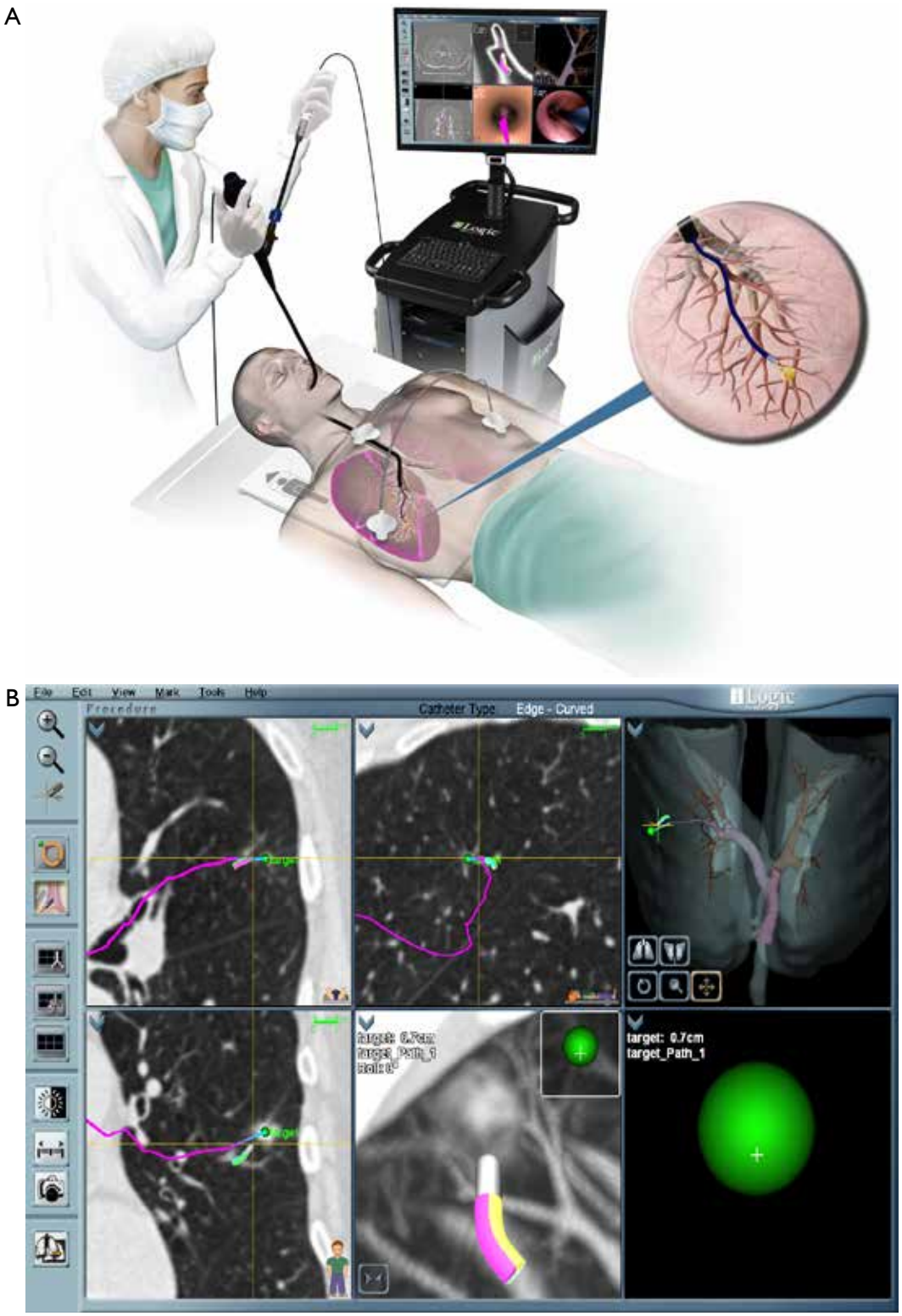

Figure 2 A. Electromagnetic Navigation Bronchoscopy (reproduced with permission from SuperDimension® ENB™); B. Screen capture of a procedure in process. The route (pink line) to the lesion is predetermined by analysis of CT chest images. The target (green sphere) is represented and distance to target is continuously updated. (courtesy Joe Cicenia, M.D., Cleveland Clinic Foundation).

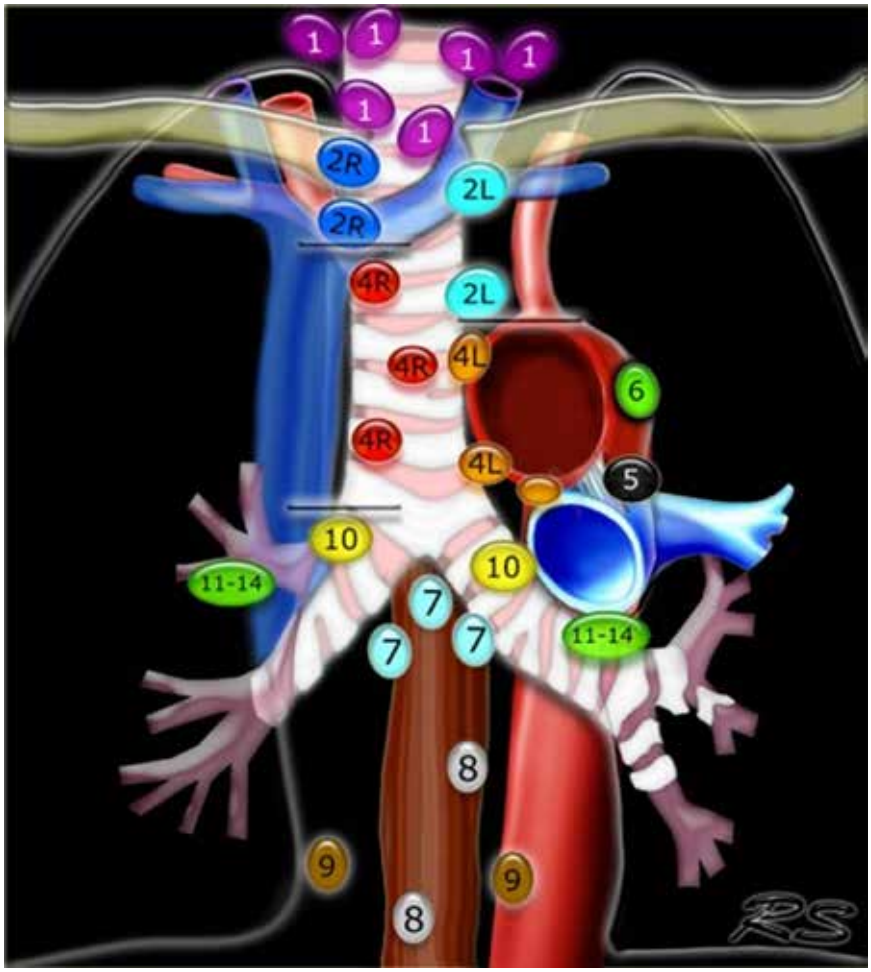

Figure 3 Regional lymph node classification for lung cancer staging based on the IASLC staging 2009 (43). (courtesy of Dr Robin Smithius www.radiologyassistant.nl).

tomography (PET) scanning followed by tissue sampling of any pathologic nodes. Depending on population prevalence, non-invasive imaging alone is inadequate as histological staging is obligatory to prognosticate and stratify management options (44,45). For example, in geographic regions where histoplasmosis infection is endemic, granulomatous infection can lead to PET-avidity in the mediastinum and lung lesions. Conversely, Altorki *et al.* conducted a retrospective review of 224 patients identified with clinical stage I NSCLC by CT and PET scan. At resection they found that 6.5% of clinical T1 patients had occult N2 disease (46).

Surgical mediastinoscopy is the gold standard for confirming CT/PET negative mediastinal metastases with a sensitivity of 78%. However, it has some limitations. Convex EBUS is a bronchoscopic technique that compliments mediastinoscopy (23) (*Table 2*). EBUS is minimally invasive, performed under conscious sedation or with general anesthesia in the outpatient setting, Lymph node sampling occurs under direct real-time ultrasound guidance with the convex probe EBUS (CP-EBUS) allowing a much greater diagnostic yield over blind sampling (47,48) (*Figure 4*). In a prospective cohort study of 108 patients, CP-EBUS-TBNA successfully sampled 163 mediastinal lymph nodes and demonstrated sensitivity and specificity of 94.6% and 100%, respectively, and a diagnostic accuracy of 96% (49). Several systematic reviews confirm equivalent sensitivity for EBUS-TNA to Mediastinoscopy (23,50-52). Yasufuku performed a prospective controlled comparison of EBUS-TBNA and mediastinoscopy in 153 patients with potentially resectable NSCLC (prevalence of N2/N3 disease 35%). They found sensitivities for mediastinoscopy and EBUS-TBNA were

Table 2 Accessibility of lymph node stations with the various biopsying techniques

Lymph node station	Mediastinoscopy	EBUS[†]	EUS[‡]	EUS-EBUS
1-2: Highest mediastinal	+	+		+
3: Prevascular + retrotracheal			+	+
4: Upper paratracheal	+	+		+
4: Lower paratracheal	+	+		+
4: Subaortic (AP window)			+	+
5-6: Para-aortic				
7: Subcarinal (anterior)	+	+	+	+
7: Subcarinal (posterior)		+	+	+
8: Paraesophageal			+	+
9: Pulmonary ligament			+	+
10: Hilar		+		+
11: Interlobular		+		+
12: Lobular		+		+
13: Segmental		+		+
14: Subsegmental		+		+

EBUS[†], convex probe endobronchial ultrasound; EUS[‡], esophageal ulrasound.

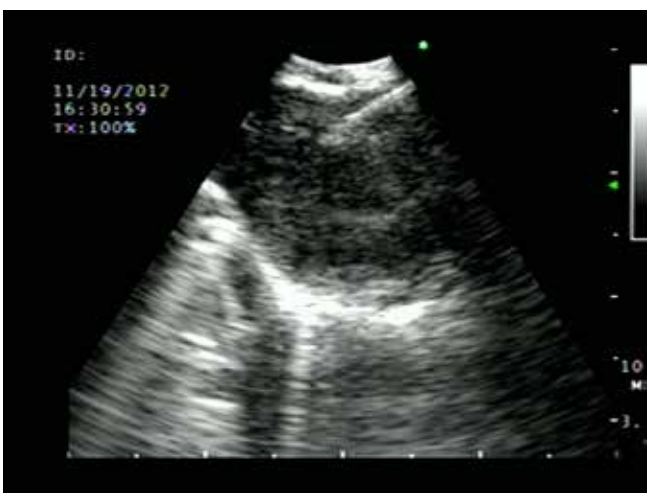

Figure 4 EBUS TBNA—Ultrasound image of real-time needle aspiration of homogenous echogenic lymph node measuring 1.5 cm.

79% and 85%, respectively, with comparable specificity (100%) and no significant differences in detecting true pathological N stage (McNemar test P=0.78) (53). In most community hospitals surgical mediastinoscopy remains the only available mediastinal staging technique. Many of the aforementioned studies were conducted at tertiary referral centers and it is uncertain how generalizable the results are.

EBUS combined with EUS/with mediastinoscopy

EBUS-TBNA has the ability to access most of the mediastinum (the anterior and superior), however the presence of paraesophageal, inferior and posterior mediastinal lymph nodes may require combined EBUS with endoscopic ultrasound guided fine needle aspiration (EUS-FNA) (*Table 2*). The combination improves the diagnostic yield compared to either procedure alone (48,54). Annema *et al.* in 2010 performed a multi-center randomized control trial in 241 patients with resectable NSCLC comparing mediastinoscopy alone with combined endosonography (EBUS-TBNA and/or EUS-FNA) approach followed by mediastinoscopy if no nodal metastases were found (55). The sensitivities of surgical staging compared to endosonography alone were 79% and 85%, respectively (P=0.47). Sensitivity improved to 94% if endosonography was followed by mediastinoscopy (P=0.02). This combined endosonographic and surgical approach resulted in greater sensitivity and fewer unnecessary thoracotomies.

Adequacy and techniques for molecular profiling

There have been dramatic advances in our understanding of the molecular makeup of NSCLCs, particularly in non-smokers or smokers with lower cumulative dose.

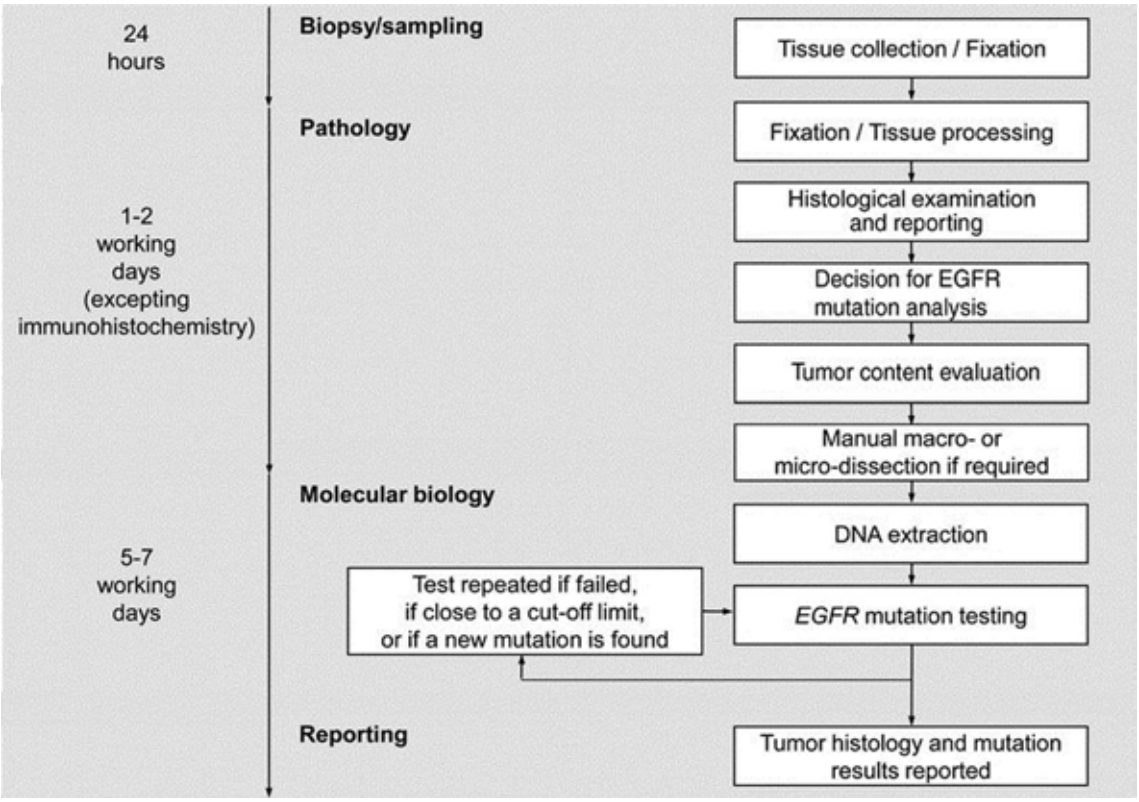

Figure 5 Sample preparation, Pathology and EGFR mutation analysis flow diagram suggested by the European EGFR workshop. *Reproduced with permission from Journal of Thoracic Oncology 2010* (69).

Driver mutations in NSCLC that can be targeted have caused a shift away from a uniform therapeutic approach to a more personalized approach (56-60). In this era of personalized medicine, there is a need to provide high quality biopsy samples not only for pathologic diagnosis but also for the detailed molecular analyses that are becoming important to patient care. Initial studies in small populations suggested that EBUS-TBNA samples can be used for molecular analysis; EGFR, K-ras, p53 and EML4-ALK mutations (61,62). Navani *et al.* conducted a large multicenter study of 774 patients and confirmed these results. While the appropriate triaging of small biopsy specimens for cytologic, pathologic, and molecular analysis is vital there are as yet no guidelines for managing EBUS-TBNA samples. It is extremely important that the bronchoscopist obtaining samples do so in a manner that optimizes the diagnostic yield from molecular analyses (63,64). Rapid on-site cytologic evaluation (ROSE) of EBUS-TBNA has been shown to increase sensitivity from 80%~88% without any added time to the procedure. Where available, ROSE allows repeated sampling of confirmed high-yield sites for triaging of specimens to cytologic diagnosis, immunohistochemisty or molecular analysis with clear communication of these goals to pathologist (61,65-68). In addition to ROSE, a few specialist centers are examining what additional procedural steps can be taken to maximize yield from small biopsy samples. This is crucial as more emerging genes are being identified that affect NSCLC carcinogenesis, such as ROS (crizotinib sensitive), Met, PI3K, etc. (61,64). As minimally invasive diagnosis and staging, as well as therapeutic modalities with driver mutations now becoming available there is increasing need to maximize and refine the technology and processes for tissue sampling (i.e., multiplex sampling, to afford our patients the best treatment options).

Re-biopsy

The European Respiratory Society (ERS) has published a statement that at biopsy it is desirable to obtain as much useful tissue as possible to avoid time consuming delays (dead time) due to molecular analysis or having to re-biopsy (69)

(*Figure 5*). In order to avoid a molecular analysis delay, many facilities have introduced reflex testing, for example any biopsy sample identified as an adenocarcinoma and as primary lung origin is automatically sent for EGFR analysis (along with other chosen molecular markers) without requiring a release from the physician. Sampling techniques, such as ROSE ensure that there is sufficient sample for these various molecular techniques, which also translates to avoiding any associated procedural delays with re-biopsy.

This does not mean however, that patients should never be re-biopsied. There is a growing realization that in patients in whom a driver mutation has been discovered there is tumor heterogeneity and dynamism. An EGFR mutant does not remain static, especially under the selective forces of EGFR-Tyrosine kinase inhibition (TKI). Although initially demonstrating a dramatic response to TKIs most patients will eventually experience treatment failure usually through acquired resistance to EGFR TKI.

Arcila *et al.* re-biopsied 121 patients with known EGFR mutations and tumor progression and discovered the T790M mutation in 70% with persistence of the original EGFR mutation in all patients (70). Similar results have been found in studies by Sequist, Oxnam and Ohashi *et al.*, including other axonal additions, deletions, SCLC conversions, BRAF mutations and many more. It is clear that identification of the molecular mechanisms will be vital to overcoming EGFR TKI resistance. It is growing apparent that a static biopsy is inadequate to guide therapeutic decision-making during a patient's treatment course. Re-biopsy at the time of disease progression is becoming standard. Pulmonologists must be available to re-biopsy at progression to assess mutational status (71-76).

Therapeutic endobronchial tumor management

Navigational bronchoscopy/RP-EBUS in fiducial placement for SBRT

Navigational bronchoscopy has been utilized to assist the radiation oncologist for stereotactic body radiation therapy (SBRT). Small peripheral lung lesions that were previously inaccessible can be sampled and fiducial markers can be placed in the same procedure in anticipation for SBRT (77,78). Standard therapy for early stage (I and II) NSCLC is a lobectomy with ipsilateral hilar lymph node dissection. While parenchyma-preserving surgeries such as sublobar resection (wedge resection & segmentectomy) have advanced over the years with improved outcomes, there is still a significant subgroup of patients with poor lung function or other comorbidities that cannot tolerate surgery (79,80). Radiation therapy for this inoperable group of patients with potentially curable disease is an attractive option. SBRT has the ability to deliver high doses of radiation with fidelity to generate margins of 1 cm. SBRT trials consistently report loco-regional and 3-year overall survival rates of 78%~87% and 55%~88% respectively, both comparable to surgery (81,82). Continuous tracking of respiratory motion using fiducials improves the fidelity of SBRT even further, allowing it to deliver beams with tumor margins of 5 mm. To date, there are three ways to deliver fiducials to or near the target lesion: transthoracic, intravascular and bronchoscopically. Currently, CT-guided transthoracic placement has been generally used, but it has a high pneumothorax rate. CT guided lung biopsy has a pneumothorax rate of 15%, while in some studies this is as high as 38%. This is certainly deleterious in a population of patients selected by their marginal pulmonary health (25,83). Intravascular placement also has its problems too. Intravascular fiducial placement cause pleurisy (13%~33%), pulmonary infarcts (5%) and groin hematomas (3%) (78,84,85). ENB placement of fiducials has the advantages of successful delivery of markers with great fidelity and with the low complication rates of bronchoscopy (*Figure 6*).

Several studies have looked at the use of radial EBUS and ENB use for fiducial placement, and have found a high success rate (Anatham found that 88% were able to be delivered to within the tumor itself) with very minimal migration of fiducials (78). Indeed, the 10% migration rate seen in studies using linear fiducials was greatly reduced if coil-spring fiducials were employed. Schroeder reported a pneumothorax complication rate of 5.3% (86). A meta-analysis by Wang *et al.* of over 3,000 bronchoscopies reports a much lower pneumothorax rate (25,87). Larger comparison studies need to confirm the role of ENB and fiducials for inoperable, early stage cancer patients. Currently, results are pending from an interventional trial-RTOG 0618-in comparing tumor control between SBRT and surgery among operable stage I/II patients.

Fiducial markers for localization for surgical biopsy

Navigational bronchoscopy can assist the thoracic surgeon with biopsy of small lesions that are difficult to palpate during video-assisted thoracoscopic surgery (VATS) or

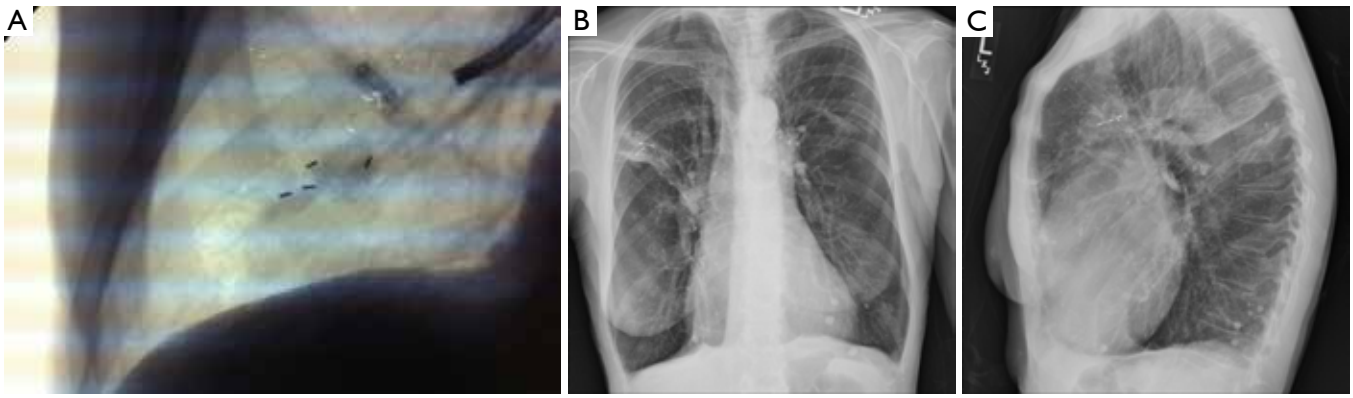

Figure 6 A. Placement of fiducial markers by bronchoscopy under navigational guidance with real-time confirmation by fluoroscopy; B. PA/LAT CXR after Fiducial Marker Placements (courtesy Joe Cicenia, M.D. Cleveland Clinic Foundation); C. Lateral.

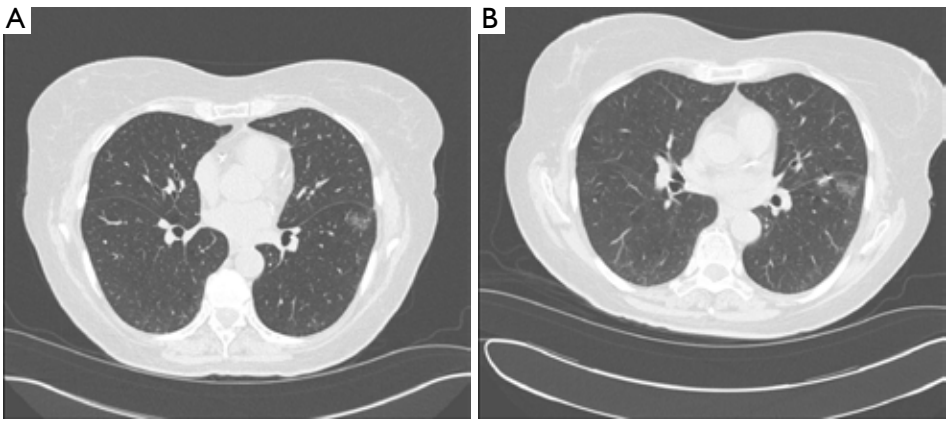

Figure 7 A. Ground Glass Nodule of Left Lower lobe (courtesy Joe Cicenia, M.D, Cleveland Clinic Foundation); B. Post-fiducial placement for in preparation of surgical biopsy (white arrow) with subsequent resection.

thoracotomy, particularly ground glass nodules that warrant histological confirmation of malignancy prior to anatomical resection or parenchymal sparing surgeries. CT-guidance can place fiducial markers with precision around the lesion prior to surgery with confirmation of position (*Figure* 7). Larger observational and interventional trials are needed to evaluate the efficacy of this complementary approach.

Palliative management in nonsurgical candidates

High dose rate brachytherapy

Henschke introduced the concept and technique of endobronchial brachytherapy in the 1960s as a method of introducing a radioactive source via a thin catheter (afterloader) intraluminally to targeted malignant tissue within the airways (16,88,89). A computerized, remote, 'afterloading' technique allows for safe delivery of radioactive material to endobronchial lesions at high doses in short periods of time while greatly minimizing radioactive exposure to staff. The most common radioisotope used is iridium-192 manufactured as a thin, flexible wire. The highly localized field of radiation around the flexible catheter allows for sparing of the surrounding tissue. High-dose rate endobronchial brachytherapy (HDREB) involves delivery of high-energy radiation over short periods (16). Although the available evidence for optimal radiation dosing is currently limited, the American Brachytherapy Society recommends 3 weekly fractions of 7.5 Gy each, 2 fractions of 10 Gy each, or 4 fractions of 6 Gy prescribed

at 1 cm (16,90). These outpatient sessions are often well tolerated and rapid with a response to therapy within 4-6 weeks (91). HDREB has shown to benefit patients with hemoptysis, dyspnea, post-obstructive pneumonia, and cough with centrally located lesions typically providing the best outcomes (16,90,91). Symptom control has been shown to be durable up to 6 months. Other potential indications for HDREB include patients who are poor surgical candidates; those who have maximized external beam radiation (EBR) doses; sole treatment for localized bronchial carcinomas; and carcinoma *in-situ* or pre-cancerous lesions (16,89,90,92). Although overall EBR alone has been more effective than HDREB in terms of durable palliation, combination of EBR with HDREB has also been shown to provide significant symptomatic control especially among patients with inoperable tumors or endobronchial obstruction causing atelectasis (89,91,93).

Photodynamic therapy

The targeted strategy of using photodynamic therapy (PDT) against malignant tissue has been in practice since the 1980s (16,94-96). It is an alternative treatment for cancer that involves administration of a systemic photosensitizing agent that preferentially accumulates in tumor cells. Palliative PDT for obstructive endobronchial tumors have been shown to be an effective strategy for patients experience persistent cough, progressive dyspnea, atelectasis and post-obstructive pneumonia (16,97-99). Results are optimal if the obstructive lesion is found in the segmental and subsegmental airways (100). PDT is generally well tolerated and can be administered regardless of prior chemotherapy, radiation or surgery. The most common photosensitizing agents used in lung cancer are hematoporphyrin derivatives, porfimer sodium (Photofrin®) and talaporfin sodium (Laserphyrin®). These agents are administered intravenously and peak extravascular concentration in tissues is achieved in 24 hours. While concentrations of the photosensitizing agent within peripheral organs decline over the next 2-3 days, tumors have been shown to selectively retain the chemical for much longer periods (16,101). For this reason the next stage of photoactivation typically does not occur until 24-72 hours when the tumor-normal tissue concentration ratio is optimal. During photosensitization a diode laser source emitting red or near-infrared light from a quartz catheter is delivered via flexible bronchoscopy to the endoluminal tumor cells. Currently the FDA recommended light dose is 200 J/cm with a total exposure time of 500 s (16,95,97,101). In addition PDT induces a thrombotic state within tumor microvessels leading to ischemic damage (16,96). As tumor cell death progresses necrotic tissue and debris accumulate in the airways in the next 48 hours after photoactivation. Repeat bronchoscopy is recommended at this point for debridement and prevention of obstruction (16,95,100). Further PDT sessions can be administered up to a maximum of 3 sessions within a 30-day period for residual tumor cells. Although PDT is generally well tolerated photosensitivity reaction in the form of sunburns can persist for up to 6 weeks after injection (16,96,101). The major disadvantage of PDT similar to brachytherapy is a delayed response after photoactivation. Thus this is not a feasible modality if rapid resolution of airway obstruction is needed (16,96,97,101).

Cryotherapy

Cryotherapy is an alternative method of controlling and debulking malignant endobronchial lesions by utilizing extreme cold energy to induce a cascade of events leading to tumor cell death (102,103). The principle of cryotherapy is the delivery of focused extreme cold energy via rapid expansion of compressed liquid nitrogen (the Joule-Thompson effect) at the tip of a cryoprobe. The high vascularity and water content of tumor tissue make it exceptionally vulnerable to extreme cold energy (16,102,104,105).

Endobronchial cryotherapy can be performed either via rigid or flexible bronchoscopy. It is considered a very safe procedure and is generally well tolerated. Patients who may be candidates for this procedure have advanced stage cancers and are poor surgical candidates. Similar to indications for photodynamic or brachytherapy, these patients require alleviation of symptoms attributed to endobronchial obstruction such as hemoptysis, atelectasis, intractable cough or post-obstructive pneumonia.

A recent systematic review noted mean response rates of 80% with minimal complications (0%~11%) (106). In a series of 476 patients by Maiwand and colleagues, palliative cryotherapy has shown to provide significant alleviation of hemoptysis, cough, dyspnea and chest pain (76.4%, 69%, 59.2%, and 42.6%, respectively) in addition to improvements in Karnofsky performance scores (59.6 to 75.2) (103,106). Although the available data have shown variable survival rates, median survival time has not shown to be worse than other palliative-focuses endobronchial therapies (102,104-106). The major disadvantage of

cryotherapy is its delayed response time and need for repeat treatments relative to other palliative endobronchial procedures such as Nd:YAG laser, electrocautery and microdebridement. Tumor necrosis may continue for days after the initial treatment. Therefore cryotherapy is not optimal for patients experiencing massive hemoptysis or extensive endobronchial tumor involvement (16).

Rigid bronchoscopy and stenting

Nearly one-third of lung cancer patients experience some form of central airway obstruction (CAO) due to external compression, endoluminal disease or bulky lymphadenopathy (107-110). The quality of life and performance status of patients with CAO is significantly compromised due to dyspnea, stridor, hemorrhage and/or obstructive pneumonias. These airway-related symptoms may preclude the operability of a patient with early lung cancer. Endobronchial stenting has been shown to significantly relieve symptoms and improve quality of life among patients with malignant obstruction (107,111). While this technique has largely been used in advanced lung cancers it is, however, a palliative method that can be utilized in early lung cancer patients with poor functional status. Furthermore early stenting in this patient population may provide an additional survival advantage in addition to symptom relief (112). This will allow those who cannot tolerate surgery to undergo other definitive treatments such as brachytherapy or external radiation.

Conclusions

The last decade has seen many advances in lung cancer diagnosis and management options. Improvements in surgical techniques such as VATS, video mediastinoscopy and parenchymal sparing surgeries; discoveries of new targeted therapies for specific gene mutations in lung adenocarcinomas; and stereotactic radiotherapy for early stage lung cancers all contribute to improvement of quality of life and outcomes for patients with variable performance status. Furthermore, low-dose CT screening for early detection of lung cancers will inevitably revolutionize how lung cancer will be approached. It is paramount that the interventional pulmonologist integrate the armamentarium of minimally invasive approaches described in this review, coupled with sound clinical judgments to collaborate with all specialists of the lung cancer multidisciplinary team.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Molecular testing in lung cancer in the era of precision medicine

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Abstract: The clinical expectations how pathologists should submit lung cancer diagnosis have changed dramatically. Until mid 90-ties a clear separation between small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) was mostly sufficient. With the invention of antiangiogenic treatment a differentiation between squamous and non-squamous NSCLC was requested. When epidermal growth factor receptor (EGFR) mutation was detected in patients with pulmonary adenocarcinomas and subsequent specific treatment with tyrosine kinase inhibitors (TKIs) was invented, sub-classification of NSCLC and molecular analysis of the tumor tissue for mutations was asked for. Pathologists no longer submit just a diagnosis, but instead are involved in a multidisciplinary team for lung cancer patient management. After EGFR several other driver genes such as echinoderm microtubule associated protein like 4-AL-Kinase 1 (EML4-ALK1), c-ros oncogene 1 , receptor tyrosine kinase (ROS1), discoidin domain receptor tyrosine kinase 2 (DDR2), fibroblast growth factor receptor 1 (FGFR1) were discovered, and more to come. Due to new developments in bronchology (EUS, EBUS) the amount of tissue submitted for diagnosis and molecular analysis is decreasing, however, the genes to be analyzed are increasing. Many of these driver gene aberrations are inversions or translocations and thus require FISH analysis. Each of these analyses requires a certain amount of tumor cells or one to two tissue sections from an already limited amount of tissues or cells. In this respect new genetic test systems have been introduced such as next generation sequencing, which enables not only to detect multiple mutations in different genes, but also amplifications and fusion genes. As soon as these methods have been validated for routine molecular analysis this will enable the analysis of multiple genetic changes simultaneously. In this review we will focus on genetic aberrations in NSCLC, resistance to new target therapies, and also to methodological requirements for a meaningful evaluation of lung cancer tissue and cells.

Keywords: Non-small cell lung carcinoma (NSCLC); molecular pathology; target (driver) genes; tissue based assessment

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Introduction

Within the last decade many important discoveries were made in the regulation of growth, differentiation, apoptosis, and metastasis of lung cancers. These findings have dramatically changed the view of the oncology community about the importance of the classification of lung carcinomas. With the findings of different responses for cisplatin treatment in adenocarcinomas versus squamous cell carcinomas (SCCs) this simple clinical lung carcinoma classification schema small cell lung carcinoma (SCLC) versus non-small cell lung carcinoma (NSCLC) was abolished. In addition, results of recent research show even the category of adenocarcinoma is in fact a heterogeneous group of different tumors with a broad spectrum of molecular changes. The chance of targeting at least some of

the mutations by currently available treatment thus requires much more precise classification of lung tumors based not solely on morphology, but including even detection of various molecular predictive markers.

Therapy relevant molecular changes in pulmonary carcinomas

NSCLC and angiogenesis

In the last decade humanized antibodies have been developed to interfere with the neoangiogenesis in primary as well as metastatic carcinomas (1,2). However, anti-angiogenetic drugs can cause severe bleeding, especially when administered in patients with centrally located NSCLC. However, it is still not clear, if the reported bleeding episodes in these patients are due to the squamous histology or more logically to the central located tumors, which are usually supported by arteries and veins arising from large branches. In addition, it was reported that cavitation within the tumor is prone to hemorrhage, again something more common in central tumors located close to large blood vessels (3). The erroneous perception of oncologists about SCCs most probably is due to the fact that SCCs arise predominantly in central bronchi.

Angiogenesis, better neoangiogenesis is a process by which primary tumors get access to nutrients and oxygen and is characterized by the sprouting of endothelial cells from the preexisting vessels (in contrast to vasculogenesis, which is the process of growth of the vessels de novo—e.g., during embryonic development). The process of neoangiogenesis is still not fully understood. Under normal circumstances endothelial cells are virtually quiescent, therefore a crucial requirement for neoangiogenesis is their stimulation to proliferation by angiogenic factors, such as vascular endothelial growth factors (VEGFs). In some cases are these factors produced by the tumor cells themselves, in other cases are these growth factors produced by elements of the immune system, such as macrophages present in the tumor microenvironment (4). However, once new blood vessels (capillaries, small arteries, veins) are formed, this provides advantage for the tumor cells over their normal neighbor cells in getting better oxygen and nutrient supply. Nutrients and oxygen are not the only important factor for rapid growth, also purine and pyrimidine bases are essential for a dividing tumor cell (5,6). Increased angiogenesis itself in invasive adenocarcinomas has a negative impact on survival and progression of disease in these patients (7).

Angiogenesis is essential for the primary tumor as well as for metastasis. The secretion of VEGFs facilitates most often neoangiogenesis. Tumor blood vessels are immature, with incomplete basement membrane, fragile, and are therefore prone to rupture. Using antibodies against VEGF (bevacizumab) the angiogenesis can be inhibited and regression of the tumor is induced. However, in some cases, mostly in centrally located tumors can this therapy result in severe hemorrhage.

New developments are focusing on the inhibition of the VEGF receptors (VEGFRs) and also on the role of hypoxia inducible factor (HIF) and hypoxia in tumor development and metastasis. In several studies the importance of VEGF and VEGFR axis was stated for vascular invasion and metastasis, mainly involving VEGF-C and VEGFR3 (7-10). Studies aiming to target this axis showed positive results in experimental settings (11-13). Bringing these targeted therapies into clinical trials is still in its infancy (14). A major problem in targeting VEGF-VEGFR is the fact that its regulation is under the major influence of the hypoxia pathway. Hypoxia is an important factor in invasion and angioinvasion, and HIF1-signaling will result in the upregulation of VEGF (15,16). So the hypoxia pathway might constantly overrule a blockade of VEGF-VEGFR unless also HIF1 production is inhibited (17). In addition, several other independent pathways regulate the angiogenesis and thus blocking of just one of them is sooner or later bypassed by another one resulting in resistance and failure of the anti-angiogenic treatment.

NSCLC and cisplatin drugs, the effect of anti-apoptotic signaling

In a large multi-institutional study the effect of cisplatin chemotherapy was investigated. High expression of deoxyribonucleic acid (DNA) repair enzymes, especially excision repair cross complementation group 1 (ERCC1) was found to be responsible for failure of cisplatin chemotherapy and this expression correlated predominantly with squamous cell histology (18). ERCC1 is part of the excision repair machinery involved in the repair of damaged DNA. In NSCLC showing a high expression of this enzyme, the action of cisplatin-based chemotherapeutics is inefficient, most probably because DNA damage induced by the drug is immediately repaired. In a subsequent report the usefulness of ERCC1 immunohistochemistry failed, probably because the antibody clone did not pick up the relevant splice variant of ERCC1. Therefore the authors suggested using messenger ribonucleic acid (mRNA)

quantification instead.

Thymidilate synthase (TS) blocker

Pemetrexed is an inhibitor of TS less for the other enzymes in the thymidine cycle. Thymidine uptake is essential for rapidly dividing carcinoma cells. In tumors with low expression of TS pemetrexed can block the enzyme resulting in growth inhibition. TS expression most often is low in adenocarcinomas, but is highly expressed in many SCCs. Thus pemetrexed is efficient in most adenocarcinomas and not in SCCs (19). However, the action of pemetrexed is still not entirely clear: thymidylate metabolism does not only rely on enzymes of the thymidylate cycle, but also needs active and passive uptake mechanisms; and thymidine uptake might also be influenced by pemetrexed (20).

Receptor tyrosine kinases (RTKs) in lung carcinomas

RTKs are membrane-bound protein receptor composed of an extracellular receptor domain, a transmembrane spanning portion, and an internal (intracellular) domain, which at its C-terminal end contains the kinase domain. The external receptor domain has a specific configuration for the binding of growth factors. Such stimulation results in dimerization of the receptor, where two molecules form either homo- or heterodimer. This specific binding changes the configuration of the whole receptor and leads to the phosphorylation and activation of the kinase domain. There are two ways of activation of RTKs in lung cancer: overproduction of ligands either by the tumor cell or by cells within the microenvironment, such as macrophages; or activation by a mutation of the receptor gene, most often within the kinase domain. The receptor kinase itself can act also in two different ways: one is transfer of phosphorylation to transfer molecules (21,22), like GAB1 or Grb2; or the kinase splits into fragments, where one activated protein fragment translocates into the nucleus and binds to specific DNA elements and induces transcription of downstream proteins (23). In lung cancer RTKs can be constantly activated by different mechanisms: amplification of the RTK gene, mutations of the RTK gene, gene rearrangements (translocation/inversion) with constant activation or inactivation of regulatory proteins. Another mechanism is downregulation of regulatory proteins by microRNAs (miRNAs), so a tumor suppressor or a negative feedback protein is not synthesized because of mRNA inactivation by miRNA (24-29).

Adenocarcinomas

Adenocarcinomas in highly industrialized countries are the most common lung carcinoma, representing up to 40% of all lung carcinomas. In addition what was previously regarded as a single entity has become a huge diversity of carcinomas. Adenocarcinomas in never-smokers most probably represent a separate entity with different etiology, pathogenesis, and gene signatures and a slower progression rate compared to adenocarcinomas in smokers. Also recent studies of gene signatures have contributed to a more heterogeneous picture of these neoplasms. Morphologically adenocarcinomas can show a variety of patterns, which in part correlate with gene signatures, although our knowledge in this respect is still in its infancy.

Adenocarcinoma is defined by the formation of papillary, micropapillary, cribriform, acinar, and solid structures, the latter with mucin synthesis-mucin-containing vacuoles in at least 10% of the tumor cells. Adenocarcinomas can be either mucinous or non-mucinous. Both will show the above-mentioned patterns. Some rare variants are fetal, colloid, and enteric adenocarcinomas. Most often a mixed pattern is seen with a predominance of at least one component.

Tumor cells in adenocarcinomas can show differentiations along well-known cell types as Clara cells, pneumocytes type II, columnar cells, and goblet cells. Due to the importance of targeted therapy the exact classification of adenocarcinomas and their differentiation from other NSCLC has become a major task in pulmonary pathology. Differentiation factors are used to prove the nature of the carcinoma especially in poorly differentiated tumors. A variety of useful markers have been tested, the most important ones are thyroid transcription factor-1 (TTF1), cytokeratin 7 and Napsin A.

Epidermal growth factor receptor (EGFR)

In 2004, an EGFR mutation was detected in a patient with lung adenocarcinoma and responded to tyrosine kinase inhibitor (TKI) treatment—a new era of targeted therapy in NSCLC has started (30,31).

Mutation of EGFR has been detected in a small percentage of lung cancer patients in the Caucasian population. These are activating mutations found in exons 18, 19, 20, and 21 of the EGFR gene (kinase domain) (32). Mutations are most often found in never smokers, females, and in patients with adenocarcinoma histology. Mutations change the configuration of the kinase, which does not need anymore the ligand-based activation from the receptor domain. The receptor stays in an activated stage and constantly signals

downstream. Proliferation of neoplastic cells in carcinomas with this activating mutation can be inhibited by small receptor TKIs such as gefitinib, erlotinib, and afatinib. These TKIs bind either reversibly or irreversibly into the adenosine triphosphate (ATP) pocket of the mutated EGFR kinase domain and thus inhibit phosphor-transfer to downstream molecules, thus blocking the signaling cascade (33). The most common mutations are deletions within exon 19 with a variation of 9-18 nucleotides, and a point mutation at exon 21 (L858R). Other less common mutations are point mutations in exon 18, and insertions in exon 20.

However, mainly within exon 20 there are also resistance mutations, the best known is T790M. This type of mutation inhibits or reverses the binding of the TKIs gefitinib and erlotinib and prevents the receptor blockade. The occurrence of T790M is most frequently associated with previous TKI treatment. This mutation can be present in the tumor cells already before the treatment initiation and becomes detectable as a result of clonal selection (overgrowth of resistant cell population) or it originates de novo. The irreversible TKI afatinib might overrule some of these resistance mutations, but more data are needed to prove this (34).

Treatment response with TKIs is best in exon19 deletions, followed by exon21 point mutation. Mutations within exon 18 and 20 are less responsive (35).

For targeted therapy with TKIs tissue samples of NSCLC have to be analyzed for these mutations. Within the different subtypes of adenocarcinomas some will show a higher percentage of EGFR mutations, whereas others not. In Caucasian population adenocarcinomas with acinar or papillary pattern are mutated in up to 27%, whereas mucinous adenocarcinomas are constantly negative for EGFR mutations (and show KRAS mutation instead). Carcinomas with biphasic morphology such as adenosquamous carcinomas and mixed small cell and adenocarcinomas can show mutations but usually in a very small percentage of cases.

Another therapy approach was tested with humanized monoclonal antibodies for EGF. By competitive binding to the receptor, this antibody replaces EGF and thus inhibits transactivation of the kinase. This type of therapy seems to be especially promising in EGFR-naïve (wild-type) adenocarcinomas and in addition also in SCCs (36,37).

Echinoderm microtubule associated protein like 4-AL-Kinase 1 (EML4-ALK1) and additional fusion partners

Inversion of the ALK1 kinase gene and fusion with the EML4 gene has been recently shown in patients with NSCLC, especially in solid adenocarcinomas with focal differentiation into signet ring cells. Subsequently other patterns have been associated with this type of gene rearrangement, such as micropapillary. Both genes are on chromosome 2; the chromosomal break is inversely rearranged whereby the kinase domain of ALK and EML4 are fused together. The ALK kinase thus is under the control of EML4, which results in a constant activation of the kinase. ALK similarly to EGFR stimulates proliferation and inhibits apoptosis. Patients with this inversion respond excellently to crizotinib treatment, which is now the second example of targeted therapy in NSCLC (38). Proof of EML4ALK1 inversion can be done with different methods: the most common is FISH where two probes (3' and 5') detecting the ALK gene on both sides of the breakpoint are used. In the normal situation these probes will detect the two portions close together or overlapping within the tumor nucleus (resulting in fused FISH signal). In cases of rearrangement, the probes will highlight each of the splitted portions of the ALK1 gene, so instead of two overlapping signals the signals split apart. In the Caucasian population EML4ALK1 rearrangement is usually found in 4%~6% of NSCLC; in adenocarcinomas this might be increased to 8%.

Other genes joining the ALK1 gene in the same way can replace the EML4 gene. If kinesin family member 5B (KIF5B) joins to ALK1, the overexpression of KIF5B-ALK (27) in mammalian cells led to the activation of signal transducer and activator of transcription 3 (STAT3) and protein kinase B and enhanced cell proliferation, migration, and invasion (27). Another fusion partner recently described is ALK-KLC1 (39). These other ALK1 fusions are rare; the incidence is about 1%.

C-ros oncogene 1, receptor tyrosine kinase (ROS1)

ROS1 is another kinase involved as a driver gene in adenocarcinomas of the lung (40). Usually the rearrangement of ROS1 is evaluated by two FISH probes for the 3'- and the 5'- ends. Only few fusion partners have been identified so far, CD74, SLC34A2, EZR, and GOPC/FIG (41,42). This gene rearrangement has no influence on outcome, but similar to ALK1 this is usually a younger population of cancer patients (43). The incidence of ROS1 rearrangement is in the range of 1%. The function of one of the fusion genes EZR-ROS was studied in a mouse model and showed that in this experimental setting the fusion gene acted as an oncogene inducing multiple tumor nodules in mice (44). Most important patients with this type of gene aberrations

responded well to the ALK1 inhibitor crizotinib (45-47).

KIF5B and ret proto-oncogene , receptor tyrosine kinase (RET)

KIF5B is one of the fusion partners for either ALK1 or RET. The KIF5B-RET fusion gene is caused by a pericentric inversion of 10p11.22-q11.21. This fusion gene overexpresses chimeric RET RTK, which can spontaneously induce cellular transformation (48). Besides KIF5B, CCDC6, and NCOA4 can form fusion genes with RET. Patients with lung adenocarcinomas with RET fusion gene have more poorly differentiated tumors, are younger, and more often never-smokers. Solid adenocarcinomas predominate, tumors are smaller but lymph node involvement is higher. The incidence of RET fusion is about in 1% of NSCLCs and almost 2% of adenocarcinomas (48-50).

Met proto-oncogene, receptor tyrosine kinase (MET)

MET is another RTK bound to cell membranes in NSCLC. The ligand for MET is hepatocyte growth factor (HGF), originally found in hepatic carcinomas. This receptor came into consideration in NSCLC because amplification of MET or alternatively upregulation of HGF was identified as a mechanism of the resistance in EGFR mutated adenocarcinomas treated by TKI (25,51). A search for the role of MET in other NSCLC excluding EGFR mutated adenocarcinomas showed, that MET amplification was a rare event, but upregulation of MET is relatively common: approximately 20% of NSCLC including adenocarcinomas and SCCs showed high protein expression, but only 2% MET amplification (Popper *et al*. in preparation). Clinical studies are in progress to evaluate the possibility to interfere with MET signaling using monoclonal antibodies. Other studies use small molecule inhibitors for MET. Since MET expression is common in EGFR mutated adenocarcinomas some studies aim to inhibit both EGFR and MET signaling pathways (52). In a phase III trial the combination of EGFR TKI and MET inhibition failed, most probably because the cut-off levels were not properly set (personal experience and Popper *et al*. in preparation).

Squamous cell carcinomas (SCCs)

SCC is defined by a plate-like layering of cells, keratinization of at least single cells, intercellular gaps and bridges (represented by desmosomes and hemidesmosomes), and expression of high molecular weight cytokeratins (CK 3/5, 13/14). There are some morphologic variants as small cell and baseloid SCC, but these have not been associated with specific gene signatures and therefore are only important in diagnostics.

The incidence of SCC has dropped in the last three decades from a major entity representing 35% of lung carcinomas to around 17%. One of the major reasons is the shift from filter-less to filter cigarettes. This has resulted in the reduction of particle-bound carcinogens and increase of vaporized carcinogens, which more easily reach the bronchioloalveolar terminal unit, inducing mainly adenocarcinomas.

In the past, SCC was mainly a diagnosis required to exclude several therapeutic options in the clinic: no pemetrexed therapy, no antiangiogenic drugs, less responsiveness to cisplatin treatment. However, this has changed within the last 3 years, as there are several emerging new targets for treatment of SCC.

Fibroblast growth factor receptor 1 (FGFR1)

FGFR1 was identified being amplified in about 20% of SCCs (53) [M. Sharp *et al*., Poster presentation, American Association for Cancer Research (AACR) meeting 2011]. In experimental studies as well as in ongoing clinical trials it was found that only amplification, proven by *in-situ* hybridization methods identified patients, who respond to small molecule inhibitor treatment (54). In subsequent trials the FGFR1-TKI therapy failed despite amplification: it became clear recently that there are additional genetic changes in some of these patients, specifically CA-PI3K mutations or amplifications. So in future the tumor in these patients will require analysis for several genes.

Discoidin domain receptor tyrosine kinase 2 (DDR2) and FGFR2

DDR2 and FGFR2 mutations are found exclusively in SCCs, however, only in a small percentage, 4% and 2%, respectively (55). In DDR2 mutated SCC patients some TKIs were successfully applied (56,57). For FGFR2 multikinase inhibitors might be an option for specific treatment (58,59).

Large cell carcinoma (LCC)

LCC is defined by large cells (nuclei >25 μm) devoid of any cytoplasmic differentiation, and large vesicular nuclei. They have a well-ordered solid structure. By electron microscopy differentiation structures can be seen such

as hemidesmosomes, tight junctions, intracytoplasmic vacuoles with microvilli, and ill-formed cilia. This fits clearly into the concept of a carcinoma, at the doorstep of adenocarcinoma and SCC differentiation. LCC numbers have dramatically decreased due to the routine use of immunohistochemistry for more precise sub-classification of NSCLC. Using TTF1, low-molecular cytokeratins, as well as p63 and cytokeratin 5/6 most cases of LCC were either reclassified into adenocarcinoma or SCC, respectively (60). These recent changes make an evaluation of genetic aberrations in LCC quite difficult, since genetic studies were based on previous classifications.

Not surprisingly EGFR mutations, MET amplifications, and EML4ALK1 fusions have been reported in LCC (61). LKB1, a gene mutated in a small percentage of adenocarcinomas was also shown in squamous and large cell carcinomas (62). LKB1, also known as serine/threonine kinase 11 (STK11), is involved in the negative regulation of mechanistic target of rapamycin (mTOR) and closely cooperates with tuberous sclerosis gene (TSC) 1 and 2 genes (63).

Resistance mechanisms

There are general classes of resistance mechanisms to TKI therapy. The target can be altered by a secondary inhibitory mutation or by amplification. The second class is a bypass track, by which the blocked TK is circumvented. Finally the tumor may undergo phenotypic and genotypic changes, which makes TKI-therapy inefficient.

The most frequent resistance mechanisms for EGFR are inhibitory mutations on exons 20 and 19. The most common ones on exon 20 are D770_N771 insertions (up to 3%) and the mutations T790M, V769L, N771T, and the D761Y mutation on exon 19 (64-66). Several of these mutations might be targeted by second and third generation TKIs (67). A common bypass track in EGFR mutated adenocarcinomas is amplification of the MET receptor (64,68,69). A third mechanism is a phenotypic change of the tumor. A transition from adenocarcinoma to small cell carcinoma has been reported. Also re-biopsies have shown a transition from a well-differentiated adenocarcinoma to an undifferentiated carcinoma (57,70-72). Concomitant to this phenotypic change also genotypic changes are seen: a SCLC no longer presents with EGFR mutation but will respond to classical chemotherapy. In transgenic mice an upregulation of pS6 might explain some of these phenomena. Two new resistance mechanisms have been reported on a recent poster session: methylation of PTEN promoter region caused a deactivation of PTEN (similar to PTEN loss) and subsequent upregulation of PI3K-AKT pathway. The second resistance mechanism was an aberrant signaling of EGFR into SRC kinases, thus circumventing the effect of EGFR blockade by TKI (Izumi *et al*., ERS Congress Munich, Sep. 6th, 2014).

Resistance mechanisms in EML4ALK rearranged lung adenocarcinomas do exist, however, the exact mechanisms are still under investigation (73,74). Most common are secondary mutations in the ALK domain. Most common are L1196M and G1269A, less common are 1151Tins, L1152R, C1156Y, F1174L, G1202R, and S1206Y (75-77). Again bypass mechanisms do occur such as MET activation, but also ALK amplification. Interestingly second and third generation ALK inhibitors can target most of the secondary mutations. However, also these new generation ALK inhibitors will induce secondary resistance mutations, for which new drugs have to be designed (78,79).

Similar to EGFR and EML4ALK also for ROS1, KIF5B, and RET secondary mutations have been reported (80,81). For MET this can be expected, but so far treatment has just started with MET inhibitors.

Resistance mechanisms for FGFR1 inhibition are still not exactly known. The major problem in this setting of SCCs is complicated, because response to treatment might be dictated by the mode of FGFR1 modification in the carcinoma: mutation, amplification, deletion, and/or multiple alterations. In lung SCCs the prevalent alterations are amplification and mutation (53,82). This has largely been ignored, therefore the outcome and response has to be reevaluated. Using TKIs for FGFR1 some carcinomas responded quite well, whereas others not. Another problem in FGFR1 amplified pulmonary SCCs is the coincidence of FGFR1 amplification with PI3K mutations and amplifications (82). These new findings have to taken into account, before resistance mechanisms can be further explored.

Treatment for DDR2 and FGFR2 mutations has been applied in few patients. A resistance mutation has already been shown in cell culture studies using cell lines with DDR2 mutation (83). So far this has not been seen in patients.

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Footnote

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