



1A040

RADIATION AND COMBINED
THERAPIES FOR LUNG CANCER

Editors: Shenglin Ma
George Rodrigues
James W. Welsh

AME Medical Book 1A040

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Room C 16F, Kings Wing Plaza 1, NO. 3 on Kwan Street, Shatin, NT, Hong Kong

Information on this title: www.amegroups.com

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First published in 2018

Printed in China by AME Publishing Company

Editors: Shenglin Ma, George Rodrigues, James W. Welsh

Radiation and Combined Therapies for Lung Cancer

(Hard Cover)

ISBN: 978-988-78919-9-4

AME Publishing Company, Hong Kong

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Radiation and Combined Therapies for Lung Cancer

(FIRST EDITION)

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Xiaoyan Hu, AME Publishing Company

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

This book addresses the role of radiotherapy in non-small-cell lung cancer (NSCLC) in the late 2010's. Is radiation oncology, a valiant hundred years old discipline, still a key-player in the management of NSCLC ? Radiotherapy in NSCLC has a long history, and its importance has been demonstrated by a large number of level I evidence-based studies on radiotherapy alone or combined with surgery and/or chemotherapy over the past four or five decades. However on the one hand, due in part to the slow overall survival improvement, and on the other hand due to the rapid progress in other disciplines, in the first place surgery and medical oncology, the role of radiotherapy in many situations has been recently challenged, and sometimes negated by well-intended experts in NSCLC. In spite of the remarkable discoveries in basic molecular mechanisms, leading to novel individualized therapies in metastatic disease, in spite of the growing knowledge in immune response, and in spite of superb developments in minimally invasive surgery, it would be a tragic mistake to ignore the extraordinary developments of radiotherapy in NSCLC. Indeed, radiotherapy continues to be a major actor at nearly all stages of NSCLC, from curative to palliative treatments. It would be also a great mistake to envisage all the recent progress in surgery, radiation oncology and medical oncology separately, since many of the major advances in the management of NSCLC at any stage in the past decades came from a multidisciplinary approach, with treatment decisions taken by all partners before any therapeutic action. Only then, the best of all disciplines can be offered to individual NSCLC patients, using optimal choices, combinations and sequencing while minimizing the risk of toxicity. Given the high-speed developments of the above-mentioned oncological fields, it is increasingly important that all specialists have a solid knowledge of their partners' disciplines, as the integration of innovations in surgery, radiation therapy and systemic treatments may be very complex, and sometimes confrontational. This is why the publication of this book *Radiation and Combined Therapies for Lung Cancer* is particularly timely and takes up this very difficult challenge. It contains 27 well-balanced and comprehensive chapters gathered together in 6 sections on radiotherapy techniques, combinations of radiotherapy and chemotherapy, radiotherapy and immunotherapy, radiotherapy and targeted therapies, radiotherapy and surgery, and sequencing of radiotherapy and chemotherapy in combination with surgery. These excellent chapters were written by a panel of international experts from North America, Europe and Asia, and will present the most recent advances in radiation oncology and its combination with other disciplines, intended not only for radiation oncologists, but also for all their partners involved in the management of NSCLC.

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As the leading cause of cancer-related death worldwide, lung cancer's significance cannot be overstated. Radiotherapy continues to be an indispensable tool in the treatment of lung cancer. For localized disease, radiotherapy can be curative, whether it is stereotactic body radiation therapy (SBRT) for early-stage disease or chemoradiation for locally advanced disease. In advanced disease, radiotherapy is one of the most effective tools for palliation of symptoms and control of brain metastasis. However, the sobering reality remains that lung cancer is a deadly disease for most who develop it, and much more progress must be made.

In recent years, multiple exciting and impactful developments have occurred in lung cancer radiation, for all stages of disease. The chapters of this book comprise an indispensable and up-to-date overview of the current state of lung cancer radiotherapy, the recent advances that have been made, and the questions and frontiers that remain to be explored.

For early-stage disease, SBRT has truly ushered in a new era of effective management for inoperable patients. It is no longer an emerging therapy but a new standard of care for those who are not surgical candidates. The question is no longer whether SBRT is effective, but whether it can be considered a suitable alternative to resection even in those patients who are eligible for surgery.

For locally advanced disease, immunotherapy has emerged as a highly promising adjunct to standard chemoradiation. Major unanswered questions include whether proton therapy has a significant clinical benefit, and whether postoperative radiation improves survival in resected patients with N2 disease. Both of these questions are the subject of ongoing multi-center randomized trials.

For metastatic disease, the emergence of targeted agents, such as tyrosine kinase inhibitors for EGFR-mutated cancers, has greatly changed not only the prognosis of certain subsets of NSCLC patients, but the role of radiation as well. The CNS activity of certain targeted agents suggests that cranial radiation need not always be first-line therapy for brain metastasis, potentially reducing the role of radiation. On the other hand, NSCLC patients with targetable mutations such as EGFR may be prime candidates for the early integration of radiation therapy, potentially increasing the role of radiation.

These brief comments only scratch the surface of the meaningful advances, impactful data, and provocative new questions that have arisen in the last few years. The articles in this book, reflecting contributions from many esteemed experts who have been at the forefront of these new developments, will provide the reader with an excellent overview of the current state of lung cancer radiotherapy. It is a distinct pleasure and honor for me to present and introduce them to you.



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Radiotherapy plays an important role in the comprehensive treatment of lung cancer, approximately two thirds of patients will be received at least one course of radiotherapy throughout their illness. In recent years, the application of radiotherapy is more extensive due to the better dose coverage of tumor targets and protection of normal tissues and organs, which mainly benefited from the rapid progress of radiation and imaging techniques. For patients with early stage non-small cell lung cancer (NSCLC) who are unfit for radical surgery, stereotactic radiotherapy (SBRT) has become the standard of care. Even the patients who were eligible for surgery, SBRT also showed promising outcomes in some retrospective studies. The issue of postoperative radiotherapy (PORT) in patients with resected NSCLC remained controversial since the PORT meta-analysis article was published in 1998. Recent studies showed that modern PORT conferred an additional survival advantage beyond that achieved with adjuvant chemotherapy alone in pathologic N2 patients. In stage IV disease, there were also accumulating evidences indicating that the application of radiotherapy in this setting not only served as a palliative treatment but also had the potential to increase survival, especially for those with limited metastases.

With regard to systemic treatment in NSCLC, significant progress has been made in recent years, including angiogenesis inhibitors, molecular targeting therapies specific for oncogenic drivers and immunotherapies. The applications of these treatments were increased in clinic practice, which produced relatively high response rate and long duration with acceptable toxicity profile. Furthermore, the life expectancy in these patients was significantly prolonged than those in the past with treatment of chemotherapy alone. In this context, radiotherapy, as a local treatment modality, has more space for development and imagination in the area of combination therapies. For example, in local advanced NSCLC with EGFR mutation, the combination of thoracic radiotherapy and oral small-molecule tyrosine kinase inhibitors produced a progression free survival of 27.9 months (RECEL study). Maintain treatment with the PD-L1 inhibitor (durvalumab) in patients with locally advanced NSCLC who have not progressed following concurrent chemoradiotherapy, showed encouraging results; the median progression free survival from randomization was 16.8 months in the randomized phase III trial (PACIFIC). Of interest, in a post hoc analysis of KEYNOTE-001 phase 1 trial, patients with a history of previous radiotherapy showed better clinical activity and got more survival benefits from the treatment of pembrolizumab, albeit most patients in this study (64%) received radiotherapy with a palliative intent. All of those indicated that combination of modern radiotherapy with novel systemic treatment deserves intensive investigation, and further work will be necessary to determine the optimal dose/fractionation, timing of radiation in order to harmonize the synergy effects.

In this book, many challenging clinical scenarios in lung cancer radiotherapy will be discussed, and recommendations based on available data or directions deserved further research will be given, including SBRT in early stage NSCLC, radiotherapy in local advanced NSCLC, cranial irradiation in specific lung cancer, and the combination of radiotherapy with chemotherapy, immunotherapy, targeted therapy and surgery.

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The health policy implications of lung cancer are significant in terms of both cancer incidence and mortality ranging from the local to international perspectives. Although the rates of smoking-related lung cancers appear to be easing among various patient populations, mortality from lung cancer continues to be high despite advancements in imaging, surgery, radiation therapy and systemic therapies. Advancements in health policy interventions, patient screening, molecular subtyping and immunotherapy may hold promise in further reversing these incidence and mortality trends.

Radiotherapy has a central and important role in the management of NSCLC to optimize patient outcomes. In resectable disease, meta-analyses and guidelines have provided important information regarding the selection of patients and dose-fractionation for post-operative radiotherapy. Similarly, four decades of clinical trial experience have clarified the indications, dose-fractionation, and use of concurrent chemoradiation for the management of locally-advanced NSCLC. More recent investigations of stereotactic ablative radiotherapy as an alternative to surgery for early stage disease have provided patients with an important option for the management of this clinical entity. Additionally, other palliative radiotherapy indications exist to optimize health-related quality-of-life and to reduce tumour-related symptoms.

In “*Radiation and Combined Therapies for Lung Cancer*” this central role of radiotherapy in the management of NSCLC is further explored by experts in the field to provide the reader a review of what is currently known for a variety of clinical NSCLC scenarios but also to look forward to where the field is potentially heading. Specifically, the areas of radiation modality and technique are explored in terms of potential improvements in the therapeutic ratio within the radiotherapy modality. Additionally, issues surrounding the inclusion and sequencing of multimodal treatment combining radiation with surgery, chemotherapy, targeted therapy, and immunotherapy are explored by multiple authors in this book.

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Lung cancer continues to contribute to the growing burden of non-communicable disease, not just in North America but around the world. With an ever-growing world population and the accumulation of genetic mutations in that population, the need for clinicians to embrace multimodality treatment is more acute than ever. The era of “personalized therapy” for all types of cancer has arrived, particularly for lung cancer, where time and time again we see some patients having positive responses to combinatory treatments, only to see others fail to respond to the same combinations. Treatment options for lung cancer are expanding rapidly thanks to advances in immunotherapy, radiation, chemotherapy, and other types of intervention. Even more unprecedented is the paradigm shift occurring in the context of radiation therapy. Radiation, long seen as solely as a means of local tumor control, is now, in combination with immunotherapy, showing promise for improving systemic control. The ability of radiation to turn a cancer into an *in situ* vaccine, acting against itself, enhances the potential of radiation as a powerful tool for treating systemic disease.

With the rapid pace of these innovations comes the need to bridge the knowledge gap, to inform the community of the countless clinicians, research scientists, and industries devoted to meeting the demands of lung cancer treatment. This textbook undoubtedly helps to bridge that gap. Written by experts from Europe, Asia, and North America, it is a crucial resource that our community needs to meet the present and future challenges of lung cancer treatment.

This textbook, while focusing on the role of radiation therapy in lung cancer management, provides chapters focusing on a broad variety of issues ranging from the relevance of proton therapy for the management of thoracic malignancies to the influence of stereotactic ablative radiotherapy and brachytherapy for the treatment of lung cancer. Its innovation extends further to chapters that outline new combinatorial advances in radiation therapy, such as combinations with immunotherapy, surgery, and chemotherapy. The work described in this book also has major translational implications with regard to the effects of sequencing and timing of radiation treatment in combination with other forms of therapy. Answers to these sorts of crucial questions are being sought by many radiation oncology clinicians today.

Lung cancer is a global threat. The GLOBOCAN global cancer statistics, last published in 2012, show that lung cancer is the most common type of cancer all over the world, with approximately 1.8 million new cases diagnosed each year, a number that continues to grow, with up to 58% of lung cancers occurring in middle- and low-income countries. Lung cancer is still the most common cancer in men worldwide and the most common cause of death from cancer worldwide. With the ever-increasing threat of pulmonary environmental pollutants comes the pressing need to disseminate knowledge on the importance of radiation therapy in the treatment of lung cancer, and we hope that our readers find that knowledge within these pages.

We are grateful to AME Publishers for the opportunity to publish this work, and for their incredible efforts in bringing this book to fruition. We hope that its readers will gain valuable knowledge on how far this field has come and can help to generate additional ideas for the future for further enhancing the effectiveness of radiation in the fight against lung cancer.



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This themed collection of articles from journals of AME (<http://amegroups.com/>) on Radiation Therapy for Lung Cancer is aiming to be broadening the horizons of all researchers interested in optimization of lung cancer treatment and is providing a spectrum to enable practicing radiation oncologists to embrace the current management in the multidisciplinary setting of patient selection and radiotherapy in lung cancer from the basics to the cutting-edge treatments. This book covers an advocacy of radiation oncology perspective equipped with knowledge, evidence and experience based advanced technology to understand the challenging surgical and medical oncology approaches in multidisciplinary tumor board. The instructive spectrum of radiotherapy in lung cancer from brachytherapy to intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), stereotactic body radiotherapy (SBRT), and proton therapy will outline the practical instructions to ease the management decisions of everyday and upcoming challenging cases. We hope “*Radiation and Combined Therapies for Lung Cancer*” will meet the need for an up-to-date practical review; and articles on lung cancer at different stages, providing an academic expert view of timing, combination, consequences, concerns, and influences of all modalities including surgery, radiotherapy, chemotherapy and immunotherapy, will be of value for practicing oncologists as well as fellows and residents interested in lung cancer treatments to facilitate the decision making in the management of their patients.



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Radiation therapy for locally advanced lung cancer

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Abstract: Management for locally advanced non-small cell lung cancer (LANSCLC), which consists of Stage IIIA and IIIB disease, has progressed throughout the decades. While overall survival (OS) remains guarded, advancements in radiotherapy techniques along with the integration of chemotherapy, including targeted therapy, is transforming modern management. LANSCLC was initially treated with definitive radiation therapy (RT) alone. Early trials showed a local control benefit and OS benefit with dose escalation using conventional and altered fractionation. The next phase of management included the addition of chemotherapy. Sequential chemoradiation led to a survival benefit, however, concurrent chemoradiation proved to be a better regimen. While definitive chemoradiation is the standard of care for LANSCLC, neoadjuvant chemoradiation followed by surgical management is reserved for a subset of patients who have low volume single nodal station disease and are eligible for a lobectomy upfront. In terms of techniques, we have progressed from treating elective nodal sites to involved nodal regions. Supplementary technical improvements include three dimensional computed tomography planning, targeting ¹⁸F-fluorodeoxyglucose positron emission tomography-computed tomography planning, motion management, use of Intensity Modulated Radiation Therapy (IMRT), and evaluating normal tissue dose volume relationships. We will also discuss ongoing novel techniques such as adaptive RT and use of hypofractionation. Finally, appropriate palliative treatment will be reviewed highlighting the role of dose per fraction, brachytherapy, and use of concurrent chemotherapy. American society for radiation oncology (ASTRO) summary guidelines will be presented at the end of the definitive and palliative section. Here, the advancement of RT for definitive and palliative treatment will be reviewed.

Keywords: Cancer; radiation; palliative; definitive

Submitted Aug 03, 2015. Accepted for publication Aug 05, 2015.

doi: [10.3978/j.issn.2218-676X.2015.08.03](https://doi.org/10.3978/j.issn.2218-676X.2015.08.03)

View this article at: <http://dx.doi.org/10.3978/j.issn.2218-676X.2015.08.03>

Definitive RT

RT alone

Definitive radiotherapy as a therapeutic strategy for LANSCLC is based on the landmark study reported by Roswit *et al.* in 1966 (1). This randomized control trial (RCT) found RT doses of 40 to 50 Gy using 1.75 to 2 Gy per fraction resulted in an overall survival (OS) benefit when compared to observation (1-year OS 18.2% *vs.* 13.9%, respectively). While OS was limited, local control

as a means of improving overall outcomes was established. Further improvement in survival was sought in the first dose escalation conducted by the RTOG. Here, RTOG 73-01 compared four radiation fractionation schemes. This included a split course regimen of 40 Gy, as well as 40, 50, and 60 Gy delivered at 2 Gy per fraction, 5 fractions per week (2). While the split course had the lowest survival (2-year OS 10%), the other dose regimens were equivalent in regards to survival (2-year OS 45%). Maturation of the data demonstrated that the 60 Gy arm, when compared to

the other conventional treatments of 50 Gy and 40 Gy had higher intrathoracic control [3-year local regional control (LRC) 67% vs. 58% vs. 56%, respectively] (3). This dose response relationship was supported by additional RTOG Trials where dose was found to correlate with an increase OS (4). Consequently, 60 Gy at 2 Gy per fraction became the standard of care for LANSCLC.

Hyperfractionation benefits

Seeking to improve upon the results of standard fractionation, various fractionation schemes were developed in an attempt to improve local control. This included hyperfractionation which is the delivery of higher doses in the same overall treatment time but with more fractions (e.g., 2 fractions per day). Total dose must be increased to account for the lower dose per fraction to achieve equivalent local control. When hyperfractionation is applied clinically, typically two fractions are delivered per day (with a 6-hour interfraction interval to allow for normal tissue repair). For example, RTOG 8311 was a phase I/II dose escalation trial using hyperfractionation. Dose was escalated using 60, 64.8, 69.9, 74.4, and 79.2 Gy at 1.2 Gy twice daily (BID) fractions (5). This feasibility study demonstrated that hyperfractionation as a means of escalating dose did not lead to a significant increase in acute or late effects on normal tissue. Also, the 69.6 Gy arm showed an improved OS in a subset of patients with stage III disease [American Joint Committee on Cancer (AJCC) 1984], $\leq 5\%$ weight loss, and Karnofsky performance scale (KPS) ≥ 70 . Hyperfractionation can also be delivered using a three fraction per day approach referred to as continuous hyperfractionated accelerated radiotherapy (CHART). CHART was explored in a RCT where 60 Gy in 2 Gy daily fractions was compared to 54 Gy in 1.5 Gy fractions given three times a day (TID) (6). The TID regimen was associated with an OS advantage, predominantly in squamous cell carcinoma histology, while again showing no difference in late dysphagia and moderate/severe pneumonitis. A follow-up dose escalation study (CHARTWEL) compared 60 Gy using 1.5 Gy TID fractions against 54 Gy using 1.5 Gy TID fractions (7). The high dose arm was associated with higher acute esophagitis and late mild pulmonary morbidity. Additionally, ARO97-1 compared the CHARTWEL regimen against 66 Gy using 2 Gy daily fractions (8). While CHARTWEL may have improved local control in those with advanced disease, when including all cohorts the OS, local control, and rate of

distant metastasis were the same.

Sequential chemoradiation therapy

Concurrent with the development of hyperfractionation regimens, the introduction of chemotherapy to the management of LANSCLC occurred. The CALGB were the first to demonstrate that induction cisplatin and vinblastine followed by 60 Gy (2.0 Gy per fraction) improved median survival for inoperable LANSCLC when compared to RT alone (13.7 vs. 9.6 months, respectively) (9). Additionally, the benefit of sequential chemoradiotherapy (CRT) was demonstrated in the Intergroup (INT) study as induction chemotherapy followed by 60 Gy in 2 Gy fractions led to an increase in median survival when compared to RT alone using 60 Gy in 2 Gy fractions and altered fractionation RT alone using 69.6 Gy with 1.2 Gy BID fractions (13.8 vs. 11.4 vs. 12.3 months, respectively) (10). These two trials established induction chemotherapy followed by 60.0 Gy at 2.0 Gy per fraction as the standard management for LANSCLC prior to the development of concurrent CRT.

Concurrent chemoradiation therapy

Though the CALGB and INT trials established sequential CRT over RT alone as the standard of care for LANSCLC, multiple concurrent CRT trials established this to be superior over sequential therapy as seen in *Table 1*. A Japanese trial included 312 patients with unresectable stage III NSCLC and compared concurrent CRT (split course RT) to sequential therapy (11). The median survival and OS was improved in the concurrent CRT arm at the expensive of increased myelosuppression. Additionally, RTOG 9410 performed a 3-arm study in patients with unresectable stage II-III B (99% were stage III) disease (12). Here, sequential CRT using conventional fractionation to 63 Gy, concurrent CRT using conventional fractionation to 63 Gy, or concurrent chemotherapy using hyperfractionation, 69.6 Gy at 1.2 Gy BID were compared. After a median follow-up of 11 years, the concurrent CRT arm was reported superior to that of sequential therapy by demonstrating an OS benefit of 6%. Several other studies contributed to the establishment of concurrent CRT to be superior to sequential chemotherapy using radiotherapy doses between 60 to 66 Gy (12-14) (*Table 1*). In 2010, the NSCLC Collaborative Group published a meta-analysis analyzing sequential and concurrent CRT

Table 1 Important definitive radiation therapy trials for Locally Advanced Non-Small Cell Lung Cancer (LANSCLC)

Trials	Pts	Arms	Conclusions
RT alone			
VA Study	800 pts Localized inoperable RCT	I. Placebo (Inert compound) II. RT alone (40-50 Gy) III. Chemotherapy	RT (compared to placebo) I. ↑ MS (112 → 142 days; P=0.05) II. ↑ 1-year OS (13.9 → 18.2%; P=0.05) III. Long term survivors* (230 → 300 days; P=0.01)
RTOG 73-01	365 pts Stage III (Included T3N0) RCT	I. Split course 40 Gy II. Continuous 40 Gy III. Continuous 50 Gy IV. Continuous 60 Gy	Split course 40 Gy lowest survival (2-year OS 10%) 3-year LRC I. Split Course 40 Gy (48%) II. Continuous 40 Gy (56%) III. Continuous 50 Gy (58%) IV. Continuous 60 Gy (67%)
Altered fractionation			
RTOG 83-11	848 pts Stage II-IV (No DM) Phase I/II	I. 60.0 Gy at 1.2 Gy BID II. 64.8 Gy at 1.2 Gy BID III. 69.6 Gy at 1.2 Gy BID IV. 74.4 Gy at 1.2 Gy BID V. 79.2 Gy at 1.2 Gy BID	All arms I. Same amount of acute and late toxicity II. Same OS Subset meeting CALGB 84-33 requirements# MS peaked at 69.6 Gy (13.0 mo)
CHART	563 pts Locally advanced, inoperable stage IA- IIIB (61% stage III) RCT	I. 60 Gy at 2 Gy Daily II. 54 Gy at 1.5 Gy BID	54 Gy at 1.5 Gy BID I. ↑ 3-year OS (13 → 20%) II. ↑ MS (13 → 16.5 mo) III. ↑ Acute severe dysphagia (3 → 19%)
Sequential chemotherapy			
CALGB 84-33	331 pts Stage III Phase III	I. RT alone II. Sequential chemotherapy → RT Chemotherapy: cisplatin (100 mg/m ² days 1 and 29) with vinblastine (5 mg/m ² weekly) RT: 60 Gy at 2 Gy fractions	Induction chemotherapy I. ↑ MS (9.7 → 13.8 mo; P=0.066) II. ↑ FFS (6.0 → 8.2 mo; P=0.041)
RTOG 88-08/ECOG 4588 (INT)	452 pts Stage II, IIIA, IIIB (95% IIIA, IIIB) Phase III	I. Standard RT alone II. Hyperfractionated RT alone III. Sequential chemotherapy → standard RT Standard RT: 60 Gy at 2 Gy daily Hyperfractionated RT: 69.6 Gy at 1.2 Gy BID Chemotherapy: cisplatin (100 mg/m ² days 1 and 29) and vinblastine (5 mg/m ² weekly)	Induction chemotherapy I. ↑ MS (11.4, 12.3, → 13.8 mo; P=0.03)
Concurrent chemotherapy			
RTOG 9410	610 pts Phase III	I. Sequential chemotherapy → using conventional 63 Gy II. Concurrent chemoradiation using conventional 63 Gy III. Concurrent chemoradiation using 69.6 Gy at 1.2 Gy BID Chemotherapy: Arms 1+2: Cisplatin (100 mg/m ² , days 1 and 29) and Vinblastine (5 mg/m ² weekly); Arms 3: cisplatin (50 mg/m ² weekly) and etoposide (50 mg PO BID)	Concurrent conventional chemoradiation I. ↑ Highest 5-year OS (10%, 16%, 13%) No different in Survival between conventional vs. altered fractionation.

Table 1 (continued)

Table 1 (continued)

Trials	Pts	Arms	Conclusions
Japan	320 pts Phase III	I. Sequential chemotherapy → RT II. Concurrent chemoradiation using split course RT Chemotherapy: cisplatin, vindesine, MMC; Sequential RT: 56 Gy continuous; Split course RT: 28 Gy → 10 day rest → 28 Gy	Concurrent chemoradiation I. ↑ Response Rates (66 → 84%; P=0.0002) II. ↑ MS (13.3 → 16.5 mo; P=0.03998) III. ↑ Myelosuppression (P=0.0001)
French	205 pts Stage III Phase III	I. Sequential chemotherapy → RT II. Concurrent chemoradiation Chemotherapy: cisplatin (120 mg/m ² days 1, 29, 57) and vinorelbine (30 mg/m ² /week) Thoracic RT: 66 Gy in 2 Gy fractions	2, 3, 4 year OS I. Sequential arm: 26%, 19%, 14% II. Concurrent arm: 39%, 25%, 21% Caveat: Although differences not significant, trend to OS benefit
Zatloukal et al.	102 pts Stage IIIA/B Phase III	I. Sequential chemotherapy → RT II. Concurrent chemoradiation Chemotherapy: cisplatin and vinorelbine RT: 60 Gy in 2 Gy fractions	Concurrent chemoradiation I. ↑ MS (12.9 → 16.6 mo, P= 0.023) II. ↑ TTP (8.5 → 11.9 mo, P= 0.024) ↑ WHO grade 3/4 toxicity
RTOG 06-17	166 pts 2×2 phase III	First randomization I. Concurrent chemoradiation using 60 Gy → Adjuvant chemotherapy × 2 cycles II. Concurrent chemoradiation using 74 Gy → Adjuvant chemotherapy × 2 cycles Second randomization I. No adjuvant cetuximab II. Adjuvant cetuximab Concurrent chemotherapy: Carboplatin (AUC 2 weekly) paclitaxel (45 mg/m ² weekly) Adjuvant chemotherapy: Carboplatin (AUC 6) and paclitaxel (200 mg/m ²) Q3weeks	74 Gy Arm I. ↓ MS (28.7 → 20.3 mo) II. ↓ 2-year OS (57.6 → 44.6%) III. Same Median PFS (11.8 vs. 9.8 mo) IV. Same 2-year LF (30.7 vs. 38.6 mo) V. Same 2-year DM (46.6 vs. 51.0 mo)
Surgical management			
INT-0139	396 pts Phase III	I. Definitive chemoradiation II. Neoadjuvant chemoradiation → thoracotomy Definitive RT dose: 61 Gy Neoadjuvant RT dose: 45 Gy Chemotherapy: weekly cisplatin 50 mg/m ² + etoposide 50 mg/m ²	Neoadjuvant chemoradiation + surgery I. Same OS (22.2 vs. 23.6 mo) II. ↑ PFS (10.5 → 12.8 mo, P=0.017) III. ↑ morbidity (2 → 8%) Subset analysis In lobectomy eligible patients, Trimodality ↑ MS (31.7 → 33.6 mo)

*, upper 25 percentile; #, AJCC 1984 stage III, ≤5% weight loss, KPS ≥70; AJCC, American Joint Committee on Cancer; AUC, area under the curve; BID, twice a day; DM, distant metastasis; ECOG, Eastern Cooperative Oncology Group; FFS, failure free survival; Fx, fractions; INT, intergroup; KPS, Karnofsky performance scale; LC, local control; LF, local failure; mo, months; MMC, mitomycin C; MS, medium survival; OS, overall survival; PO, oral intake; PFS, progression free survival; pts, patients; Q3weeks, every 3 weeks; RCT, randomized control trial; RT, radiation therapy; RTOG, radiation therapy oncology group.

trials concluding that concurrent CRT provides an OS benefit (5.7% at 3 years; 4.5% at 5 years) nevertheless at the cost of increased acute grade 3 or 4 esophageal toxicity (18% *vs.* 4%) (15).

Multiple chemotherapeutic agents have been delivered concurrently with radiotherapy however platinum based dual agents are standard with carboplatin and paclitaxel often favored over cisplatin and etoposide given the lower toxicity profile (16,17). Additionally, dosing has varied from weekly to full dose every-3-weeks (Q3weekly) regimens. Belani *et al.* randomized 404 patients with LANSCLC treated with definitive concurrent CRT to either carboplatin with weekly paclitaxel or Q3weekly paclitaxel and carboplatin (18). Both arms had similar median survivals and time to progression. The weekly paclitaxel arm had more grade 3 or 4 anemia and the Q3weekly arm had more neuropathy and arthralgia. The authors concluded both treatment strategies were acceptable.

However, given the low survival after definitive management, consolidative chemotherapy was studied to improve these outcomes. The Southwest Oncology Group (SWOG) phase II S9504 trial demonstrated promising results using consolidative docetaxel after concurrent chemoradiation for stage IIIB patients (19). The results showed a 3-year OS of 37% and a median survival of 26 months. However, the Hoosier Oncology Group conducted phase III trial evaluating the use of consolidative docetaxel after concurrent chemoradiation therapy and no survival difference was seen (20). Therefore, while consolidative chemotherapy is often given after concurrent chemoradiation therapy for stage III patients, there is no randomized evidence to support routine use. A recent meta-analysis, however, did show maintenance chemotherapy for advanced non-small lung cancer may increase progressive free survival and OS (21).

Surgical management for locally advanced NSCLC

While definitive CRT is standard for the majority of LANSCLC, surgery remains an option for a limited subset of Stage IIIA disease. The INT-0139 trial compared neoadjuvant concurrent CRT using 45 Gy in 1.8 Gy fractions followed by surgical resection versus definitive CRT therapy alone (22). The final results showed no difference in OS between both groups. However, an unplanned subset analysis suggested that those who were eligible for a lobectomy (versus pneumonectomy) had an improvement in median survival (33.6 *vs.* 21.7 months). Additionally, a French study analyzed 702 patients with

resected N2 disease and stratified based on clinical staging, single nodal involvement, or multi-station nodal involvement (23). The authors reported that single station, microscopic N2 disease had the highest 5 year OS (34%) while clinically positive, multistation N2 disease had limited outcomes (3%). From these series, surgical management is favored for stage IIIA patients with low volume, single nodal station disease, that are eligible for a lobectomy prior to the initiation of systemic therapy. In terms of neoadjuvant treatment, the radiotherapy dose should be between 45 and 54 Gy (24).

Dose escalation

Efforts to improve OS in the setting of definitive concurrent CRT have focused on dose escalation as a means of improving local control and subsequent survival. In 2001, a phase I/II trial for dose escalation with concurrent chemotherapy in unresectable stage IIIA/B NSCLC demonstrated the feasibility of dose escalation from 60 to 74 Gy with concurrent and induction carboplatin and paclitaxel with only 8% grade 3-4 toxicity (25). In 2004, a second phase I dose escalation trial with concurrent chemotherapy for unresectable stage III NSCLC evaluated doses from 78 to 90 Gy (26). Here, dose escalation to 90 Gy was achieved without dose-limiting toxicity and grade 3 esophagitis occurred in only 16%. These data lead to a recent dose escalation trial using concurrent CRT followed by consolidative chemotherapy. Specifically, RTOG 0617 trial was a 2x2 study evaluating 60 Gy against 74 Gy and the addition of consolidative cetuximab along with concurrent and adjuvant carboplatin and paclitaxel (27). The study was powered to detect a median survival benefit of 7 months. Surprisingly, the study was halted after an interim analysis reported the 74 Gy provided no benefit in terms of survival and potentially was detrimental.

Several explanations for the poor survival in the 74 Gy arm have been postulated (28,29). Interestingly, the inferior survival could not be accounted for by treatment-related deaths, local control, or distant metastasis between the high dose and low dose arms. There may have been uncaptured grade 5 deaths at community sites. Discrepancies in causes of mortality on death certificates and autopsy reports have been reported in the literature, and can happen in up to 47% of cases (30). This theory is supported by the heart V5 and V30 being linked to OS on multivariate analysis. Moreover, heart and lung dose constraints were suggested but not enforced and only half of the centers used intensity

modulated radiation therapy (IMRT). For centers using IMRT, poor dose calculations and variable heart contours could have affected dosimetric outcomes. The high dose arm had poorer heart contours than the low dose arm (28). Perhaps requiring proper dose constraints for critical organs at risk, necessitating use of IMRT, and providing standard organ contours could have produced different results.

Movsas *et al.* reported on patient quality of life (QOL) in RTOG 0617 (31). QOL was measured using a Physical Well Being, Functional Well Being, and Lung Cancer Subscale index. While the final results showed no difference in treatment related morbidity, patients in the 74 Gy had a significant lower QOL at 3 months than the 60 Gy arm. The authors also reported baseline QOL was a predictor for survival. However, IMRT was associated with a higher QOL over 3D-CRT. These findings lead the authors to conclude IMRT may improve the therapeutic window for LANSCLC.

The choice of chemotherapy regimens could have influenced the survival outcomes as well. The increase in mortality in the high dose group commenced within 3 months of being randomized. During this period, patients would be receiving consolidative paclitaxel and carboplatin. It is known sequential taxanes after radiotherapy increases toxicity including pneumonitis (32). This is supported by the fact less patients completed consolidative chemotherapy in the high dose arm. Perhaps different chemotherapy regimens should be used in the adjuvant setting.

Finally, the longer treatment time using conventional fractionation may have contributed to the survival difference in the high dose arm. It is known longer treatment times may lead to poor survival for advanced NSCLC patients (33). The longer treatment time could allow for tumor re-population. In CHART, 54 Gy given in 1.5 Gy BID fractions (2.5 weeks) provided a survival advantage over 60 Gy in 2 Gy fractions (6 weeks) (6). The shorter treatment time accounted for tumor re-population. Shorter treatment times with equal dose equivalence via use of hypofractionation may overcome this concern.

While RTOG 0617 did not show a benefit for high dose radiation, other factors could have contributed to the final results. Therefore, the concept of dose escalation should not be abandoned especially given the rapid advances in RT including IMRT, 4D-CT simulation scans, motion gating, image guided therapy, adaptive RT, and use of hypofractionation. Utilizing these techniques in addition to stricter protocol requirements in the setting of dose escalation, and alternative adjuvant chemotherapy

options, may provide more favorable results.

Concluding remarks and ASTRO guidelines

Therefore the ideal radiotherapy dose with concurrent chemotherapy for LANSCLC is between 60 Gy to 66 Gy with no randomized benefit seen above 60 Gy. Higher doses close to 74 Gy are associated with inferior outcomes. If concurrent CRT cannot be delivered consideration of sequential therapy or RT alone can be advocated, of which altered fractionation may be an option. If not, 60 Gy using 2 Gy fractions is the most appropriate regimen. If the patient is lobectomy eligible, a dose of 45 to 54 Gy with concurrent chemotherapy is acceptable in a select subset. The ASTRO guideline statements conclude that the standard RT given with concurrent chemoradiation therapy is 60 Gy in 2 Gy daily fractions over 6 weeks (34). If RT alone is utilized, a minimum dose of conventional fractionated 60 Gy is recommended to optimize local control. Altered fractionation has been explored with RT alone and has a strong recommendation. A summary of the landmark studies is provided in *Table 1*.

Radiation therapy techniques

CT-based treatment planning

Prior to the advent of computerized tomography (CT), 2-D lung treatment planning was performed using planar radiographs to define the field boundaries and dose calculation was performed in a single plane using rough measurements of the patient's body contour. This dose calculation also ignored tissue density changes in the lung.

Three-dimensional treatment planning based on CT scans enabled more accurate definition of target volumes and more accurate dose calculation accounting for tissue heterogeneity. In CT-based treatment planning, the gross tumor volume (GTV) is outlined, and a margin is added to include suspected microscopic spread of disease, creating the clinical target volume (CTV). To obtain the planning target volume (PTV), an additional margin is added to account for setup error and intrafraction tumor movement. Three-dimensional planning also allows detailed evaluation of doses received by tumor targets and by adjacent organs using Dose Volume Histograms (DVHs). Both institutional as well as a SEER analysis suggest that 3D treatment planning improves survival (35,36).

Volume delineation with CT-based treatment planning

When treating nodal areas, we have progressed from using Elective Nodal Radiotherapy (ENRT) to involved field irradiation (IFI). ENRT was used given the risk of microscopic disease harboring in the neighboring hilar and mediastinal nodal areas. Previous surgical series have shown occult mediastinal metastasis can be found in 20% of clinically node negative patients (37). However, treating elective nodal areas leads to larger treatment volumes which increases the risk of normal tissue toxicity. Also, there was published data in which 524 patients with NSCLC treated with IFI using 3D conformal RT had a 2-year elective nodal control of 92.4%. This control was likely due to incidental radiation eradicating subclinical microscopic disease as discussed below (38).

Yuan *et al.* addressed whether ENRT is equivalent to IFI in a RCT in which 200 inoperable stage III NSCLC patients treated with concurrent CRT were randomized to receive ENRT or IFI (39). Patients receiving IFI had higher local control, higher response rates, and decreased pneumonitis, but were treated to higher doses. The out of field recurrence rates were equivalent between both groups. This led to the prevalent adoption of treating involved nodal groups only.

In regards to adequately covering microscopic disease from the primary tumor, the histology determines the extent of CTV. Surgical series have shown local microscopic extension is larger for adenocarcinoma than squamous cell carcinoma (40,41). Given these differences a margin of 8 mm is suggested for adenocarcinoma and 6 mm for squamous cell carcinoma.

Targeting PET/CT

The advent of the 18F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) has greatly assisted in target delineation. PET-CT scans are superior to CT or PET alone for detection of mediastinal nodal metastasis (42). When compared to conventional CT scans, PET has increased sensitivity from 61% to 85% and increased specificity from 79% to 90% in regards to detection of lymph node metastasis (43). Registration of PET-CT scans to the treatment simulation CT has also led to greater consistency for defining the GTV (44). This can allow for IFI to be more confidently delivered. The PET-START trial was the first RCT to compare PET-CT treatment planning to standard treatment CT planning (45).

Results included an increase in the amount of stage IV patients identified and a trend in OS for those who received combined CRT therapy in the PET-CT group.

While PET-CT has these advantages, it has limitations seen in high false positive results for clinically node positive patients and thus should not be used to replace surgical mediastinal staging (46). There is currently an open phase II trial utilizing PET-CT for adaptive RT which will be discussed later.

Motion management

Respiratory movement has always been a major concern in thoracic irradiation (47). Unfortunately, tumor movement takes place throughout the respiratory cycle. This leads to the possibility of the tumor missing significant amounts to dose throughout the course of treatment. It also leads to artifact formation in CT scanning resulting in difficulty contouring the GTV. Due to these concerns, proper motion management techniques are recommended for movement greater than 5 mm in any dimension.

Historically, tumor motion was accounted for by adding a margin around the CTV to create the internal target volume (ITV). This becomes challenging for tumors with significant respiratory motion, such as those near the diaphragm, where superior-inferior motion can be more than 3 cm (48). The additional ITV leads to a large treatment volume which increases the risk of normal tissue toxicity and limits the ability for dose escalation. However, motion management accounts for tumor motion which allows for dose escalation without the added risk of increased toxicity (49). Several methods for motion management exist but can be broadly categorized into respiratory gating or tumor tracking techniques. We will discuss respiratory gating first and then tumor tracking techniques.

Many respiratory gating techniques utilize four dimensional CT (4D-CT) scans. This process involves a simulation CT scan during which multiple images (typically 10-12) are obtained throughout the respiratory cycle at each axial slice (50). The abdominal motion, as a surrogate for the respiratory cycle, is recorded concurrently during this process for appropriate temporal correlation. This surrogate motion may be recorded, for example, by a camera system measuring the motion of a reflective marker on the patient's abdomen, or by measuring pressure changes in a belt placed around the patient's abdomen. The signal from the abdominal surrogate is then used to bin the CT images, resulting in series of separate CT scans for each phase in the

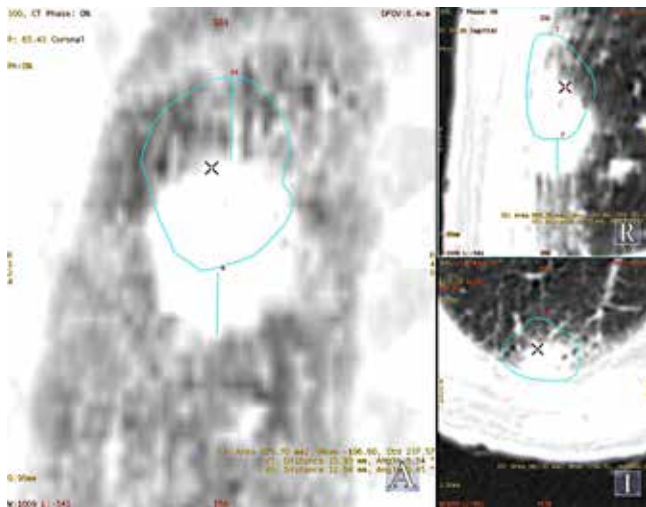


Figure 1 This CT image shows the difference in tumor location during the respiratory cycle and the importance of motion management. The blue contour shows the original tumor location at maximum expiration. If no motion management was performed, then a significant amount of the tumor may be missed during treatment and more radiation may go to normal lung. CT, computerized tomography.

breathing cycle. These scans can then be viewed in a movie loop to show how the tumor moves.

The appropriate phase window for treatment, one in which the total tumor motion is limited to a defined threshold (for example, total motion ≤ 5 mm) is identified. The treatment window is typically near the end of exhalation, since this tends to be the longest and most reproducible part of the breathing cycle. During treatment, an equivalent abdominal surrogate signal is used to control the beam on time of the linear accelerator. Choosing a narrower phase window will produce a tighter limit on tumor motion, but it will also lengthen treatment.

Abdominal compression may also be used to decrease the amount of diaphragmatic motion which in turn reduces respiratory tumor motion. The compression technique has the advantage that the treatment beam on time is not limited to just part of the breathing cycle, so overall treatment times may be shorter than those for gating. However, compression may be uncomfortable for patients, particularly those whose respiration is already compromised.

Another respiratory motion management technique is active breath control (ABC). In this procedure, the patient breathes through a digital spirometer which is connected to a balloon valve (51). The system can suspend the patients

breathing at a specified lung volume, typically at deep or moderate inhalation (52,53). After taking a few preparatory breaths, the patient is asked to breathe in to a fixed volume indicated by a video display. The valve is then closed for a patient-dependent period (typically 15-30 seconds), during which irradiation of the tumor takes place.

Another means of accommodating respiratory motion is to reposition the radiation beam dynamically so as to follow the tumor's changing position, referred to as real-time tumor tracking (54,55). Real-time tumor tracking can be achieved by using a dynamic MLC or a linear accelerator attached to a robotic arm (55). This technique requires continuous monitoring of the position of the tumor (or surrogate), which may be accomplished by tracking fiducial markers or direct fluoroscopic imaging of the tumor.

Regardless of the method, motion management is a promising technique which can allow for appropriate dose delivery to the actual tumor site while sparing critical organs at risk. *Figure 1* shows an example of the importance for motion management.

IMRT

IMRT is gaining popularity in the treatment for various malignancies (56). This technique results in increased conformity and greater sparing of normal tissue than three dimensional conformal radiation therapy (3D-CRT) (57,58). This allows for decreased rates of treatment related toxicity. Yom *et al.* published a retrospective review of advanced NSCLC treated with CRT comparing those treated with IMRT against 3D-CRT. IMRT resulted in reduced levels of grade 3+ pneumonitis. Liao *et al.* previously published a retrospective review comparing IMRT against 3D-CRT (59). Lower rates of grade 3 or higher pneumonitis were reported in the IMRT group which was thought to be secondary to a lower lung V20 value. While the V20 was higher in the 3D-CRT group, the V5 was higher in the IMRT group. These data suggest that IMRT is associated with reduced treatment related morbidity. This in return can lead to higher rates of treatment compliance. This coincides with an ASTRO Abstract published on QOL in the dose escalation RTOG 0617 study (31). This secondary analysis evaluated patient reported outcomes and its effect on survival. Interestingly, while no significant difference in toxicity between the high dose and low dose arm was found, lower patient reported QOL was more prevalent in the high dose arm at 3 months and was associated with a decrease

in survival. IMRT use was also associated with less QOL decline than 3D-CRT. This gives grounds for future phase III trials evaluating IMRT *vs.* 3D-CRT in the treatment for LANSCLC.

However there are concerns for IMRT delivery. IMRT has steep dose gradients potentially risking decreased coverage for a moving target. This disadvantage can be accounted for by gating technology as discussed above. Second, IMRT leads to more low dose spillage. Lastly, the more accurate target definition may provide a potential disadvantage. While 3D-CRT fields are conformed to the target, other mediastinal lymph nodes not contoured but in the path of the beam will receive a significant dose (60). This incidental irradiation is suggested to eradicate subclinical microscopic metastasis regional nodal stations (38). This suggested benefit in 3D-CRT may be lost with highly conformal irradiation with steeper dose gradients. *Figure 2* shows a dosimetric comparison of 3D-CRT and IMRT for a LANSCLC patient.

Organs at risk

Maintaining proper dose constraints for the lung, esophagus, and heart are critical to decrease treatment related morbidity associated with CRT. Graham *et al.* showed the lung volume receiving 20 Gy (V20 Gy) was a predictor for radiation pneumonitis and grade 2 or higher can occur in 36% of patients if the V20 Gy exceeds 40% (61). Other reports show a reduction in radiation pneumonitis when V5 Gy \leq 60%, V10 \leq 50%, V30 \leq 18 Gy and mean lung dose (MLD) is less than 17 Gy using conventional fractionation (62-65). We therefore recommend keeping the MLD <17 Gy, V5 \leq 60%, V10 \leq 40%, V20 <30% to keep the grade 2 or higher toxicity to less than 11%.

Additionally, excessive esophageal dose leads to increased morbidity and mortality. Singh *et al.* evaluated predictors for radiation induced esophageal toxicity in patients with NSCLC. He reported 58 Gy was the threshold dose for acute grade 3-5 esophageal toxicity for those who received concurrent CRT (66). Takeda *et al.* also showed the volume receiving greater than 35 Gy was a predictor for acute toxicity for both NSCLC and small cell lung cancer patients treated with thoracic radiation (67). The literature suggests esophageal volumes receiving above 40 to 50 Gy correlates with acute symptoms and the prescription dose should be the maximum dose allowed to the esophagus (68).

Heart constraints are also important. In 2010, a SEER analysis reported on over 34,000 patients treated with

chemotherapy and/or radiation for NSCLC between 1991 to 2002 (69). The large retrospective review identified an association with CRT treatment and the development of ischemic heart disease, cardiomyopathy, and cardiac dysfunction. Left sided tumors treated with radiation therapy alone were associated with an increased risk of heart failure. While there is a paucity of data regarding heart dose constraints for patients treated specifically for LANSCLC, the recent RTOG 0617 trial showed the V5 and V30 heart constraints influenced survival (27). In this trial, the recommended constraints were V60 Gy <33%, V45 Gy <66%, and V40 Gy <100%. However, adequate heart dose constraints will need to be defined and confirmed to assure the best therapeutic ratio for LANSCLC. Acceptable heart dose constraints are V30 Gy \leq 50% and V45 Gy \leq 35% to reduce the risk of pericarditis (70).

Future of definitive radiation therapy

Adaptive radiation therapy

Despite multidisciplinary advances for lung cancer management, local control and survival remain low. Escalating the radiotherapy dose may improve local control, however, there are limitations given the need to respect normal tissue toxicity. One method of combating this dilemma is through the emerging technique of adaptive radiation therapy. In this technique, a PET-CT is obtained during the treatment course. The initial course of radiation therapy uses the GTV identified on initial staging scans. However, a repeat PET-CT is obtained after a defined dose and the cone down dose is delivered to the residual FDG avid volumes. University of Michigan conducted a pilot study in 2007 to assess whether tumor and lung metabolic response during treatment correlated with post-treatment responses using PET-CT scans (71). After 45 Gy, 73% of the patients had a partial response and 13% had a complete response. The qualitative response after 45 Gy correlated with the overall response after radiation. The same group had a follow-up prospective study evaluating the use of dose escalation in adaptive planning showing adaptive RT allowed for a significant reduction in treatment volumes and allowed for dose escalation with a range of 30-102 Gy (mean 58 Gy) to be safely administered (72).

RTOG 0116 is a going randomized phase II trial evaluating Adaptive Radiation Therapy using a FDG PET-CT scan during treatment. This trial consists of stage IIIA and IIIB NSCLC patients. The control arm will receive 50 Gy

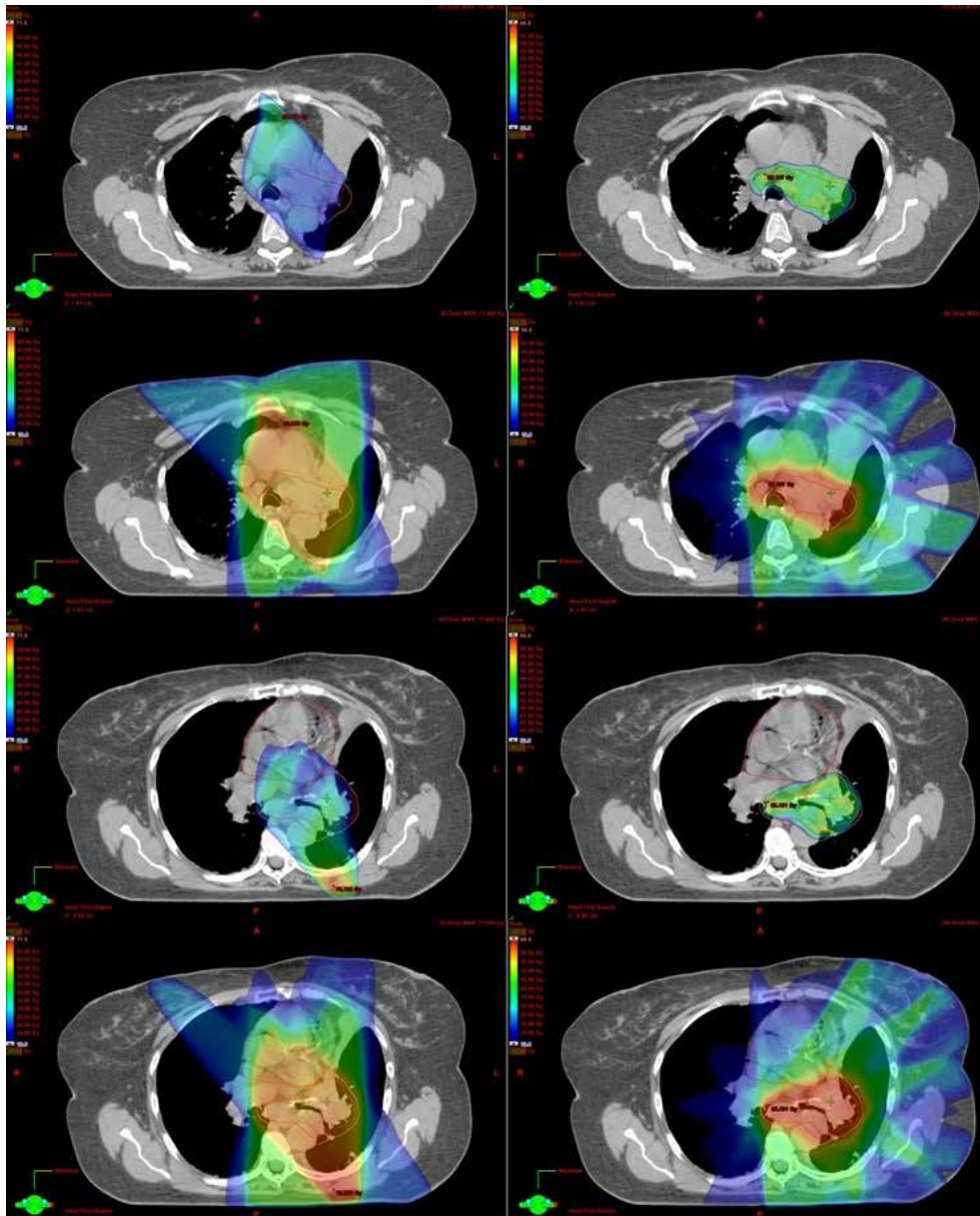


Figure 2 3D vs. IMRT for locally advanced NSCLC. The patient was treated to 60 Gy with concurrent chemotherapy. The 3D plan is on the left and the IMRT plan is on the right. Notice IMRT has greater sparing of the esophagus and heart from high dose radiation. However, 3D-CRT has less low dose spread out. IMRT, intensity modulated radiation therapy; NSCLC, locally advanced non-small cell lung cancer; CRT, chemoradiotherapy.

in 2 Gy fractions, receive a FDG PET-CT scan, and then continue therapy to 60 Gy. The experimental arm will receive 46.2 Gy using 2.2 Gy fractions, receive a FDG PET-CT scan, and then receive adaptive radiotherapy based on the new PET metabolic tumor volume up to a total dose of 80.4 Gy.

Hypofractionation

NSCLC cells have a cell doubling time of approximately 3 days and accelerated repopulation during radiation therapy is well described (73). Each additional daily treatment after 6 weeks of treatment is associated with a

1.6% decrease in survival (74). This concept is so important that it's postulated to be one of the reasons the high dose arm had a poorer survival in the RTOG 0617 trial. Hypofractionated radiation therapy may provide a valuable option to overcome this hurdle. Using this technique an equivalent or higher biological equivalent dose (BED) may be given in an equal or shorter treatment time. While there are concerns with organs at risk with this technique, hypofractionation has been shown to safely and effectively allow for dose escalation when given with or without concurrent chemotherapy for advanced stage NSCLC (73,75). The fraction dose given with chemotherapy has ranged from 2.4 to 3.0 Gy (73).

The EORTC phase I/II hypofractionation trial used 2.75 Gy fractions to a dose range of 60.5 to 66 Gy with concurrent cisplatin (76). The majority of these patients were advanced stage. This feasibility study showed low rates of both acute and late toxicity. The 2-year local disease-free interval rate was 58%. The follow up EORTC Trial which compared sequential versus concurrent chemotherapy with hypofractionated radiotherapy also had promising results (77). This trial used 2.75 Gy fractions. The authors reported low rates of both acute grade 3 or 4 hematologic toxicity and esophagitis and low rates of late grade 3 or 4 pneumonitis and esophagitis. Both of studies consisted predominately of advanced staged patients and used single agent chemotherapy. However, the SOCCAR Trial used dual agent chemotherapy and only consisted of stage III NSCLC (78). This phase II trial used 2.5 Gy per fraction up to 55 Gy and randomized between sequential and concurrent chemotherapy. Early results show treatment related mortality to be 2.9%, grade 3 or higher esophagitis to be 8.8%, and the 2-year OS to be 50% in the concurrent chemotherapy arm.

We know from previous trials, hyperfractionation using BID or TID allows for successfully dose escalation with a survival benefit. However, hypofractionation has the benefit of providing these same advantages while being more convenient for the patient. It is also important to note, given the higher dose per fraction, conformal techniques such as IMRT, motion management, and image guided therapy should be employed to ensure our best efforts of decreasing normal tissue toxicity.

Palliative

Patients with stage IV NSCLC are often treated with palliative radiotherapy to alleviate symptomatic burden. Indications for this form of therapy include dyspnea,

bronchial obstruction, hemoptysis, superior vena cava syndrome, and pain (34,79).

Different dose schedules have been evaluated in multiple randomized controls; each showing hypofractionated radiation therapy can provide adequate palliation (80-82). Common dose schedules used are 30 Gy in 10 fractions, 20 Gy in 5 fractions, 17 Gy in 2 weekly fractions, and 10 Gy in 1 fraction (34). Higher dose regimens are associated with higher rates of symptomatic improvement, more prolonged palliation, and a modest improvement in survival principally with those with a good performance status (34,83,84). However, this is at a cost of increased toxicity such as esophagitis. More succinct fractionation schedules (e.g., 20 Gy in 5 fractions, 17 Gy in 2 weekly fractions, and 10 Gy in 1 fraction) have also shown to provide adequate relief with decreased rates of toxicity (34). These shorter schedules also have an added benefit of shorter delays to chemotherapy and thus can be more efficiently assimilated between cycles.

Endobronchial brachytherapy has also been evaluated and reviewed as palliative treatment for NSCLC. This technique has the advantage of delivering high dose irradiation to a localized luminal tumor through a catheter. There is no standard dose/fractionation regimen although a range from a single fraction of 10 to 15 Gy to quadruple fractions of 3.8 Gy has been reported (85-87). Endobronchial brachytherapy is able to deliver a higher dose per fraction with a more rapid dose falloff. This aspect of treatment has a theoretical advantage of allowing for higher rates of symptomatic improvement with lower rates of normal tissue toxicity. Interestingly however, a 2006 Cochrane meta-analysis showed external beam radiation therapy (EBRT) is superior to brachytherapy for initial palliation and there is no additional advantage to combined modality (88). However endobronchial brachytherapy remains a valuable treatment option for those who have progressed through prior palliative EBRT, irradiation needed for a previously irradiated area (whether definitive or palliative), or lung obstruction in a non-metastatic patient with attempts to expand the lung for definitive treatment (34).

Concurrent chemotherapy for palliative external beam radiation therapy

Palliative radiation therapy has the benefit of providing relief in a shorter period of time than chemotherapy. Given systemic chemotherapy combined with radiation

therapy has improved outcomes for those with LANSCLC, the question arises if the same is true for those needing radiation therapy for palliative intent. There are several studies evaluating the feasibility and outcomes of this question, albeit, with variations in systemic agents, radiation schedules/doses, and patient factors (89-91). However, there is an Australian RCT designed to specifically answer this question. After randomizing 200 patients to palliative radiation therapy with or without chemotherapy, the authors concluded the addition of chemotherapy resulted in a higher radiographic response rate with no improvement in palliation, OS, or disease free survival (92). There was also a significant increase in toxicity for combined modality. The study is limited, however, in that an uncommon chemotherapy for LANSCLC was given (fluorouracil), radiographic response was measured by plain radiographs, and patients received a high dose per fraction (4 Gy × 5 fractions).

Therefore the question of concurrent chemotherapy remains unanswered given trials evaluating the use of more contemporary chemotherapy agents is sparse. Although, agents such as bevacizumab and gemcitabine are discouraged (34).

In summary, there is no data which can definitely suggest a benefit to the addition of systemic chemotherapy to palliative radiation. The therapeutic ratio is narrow and the treating Radiation Oncologist should attempt to sequence chemotherapy and radiation therapy as best as possible to provide optimal treatment outcomes with minimal side effects.

ASTRO guidelines for palliative thoracic radiation therapy

ASTRO states short fractionation schedules provide adequate symptomatic alleviation and can be used for patients with poor performance status or those requesting shorter treatment times (34). Higher dose schedules (e.g., 30 Gy in 10 fractions equivalent or greater) may provide a survival benefit for those with a good performance status and is associated with an increase in total symptom score. There is no proven additional benefit to concurrent chemotherapy. There is no concrete randomized evidence to recommend endobronchial brachytherapy with or without other palliative therapies for routine *initial* palliative management for symptomatic NSCLC tumors. Although, it is a reasonable option as a palliative therapy for previous irradiated areas.

Acknowledgements

None.

Footnote

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

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Cite this article as: Bernard ME, Clump DA, Lalonde R, Beriwal S. Radiation therapy for locally advanced lung cancer. *Transl Cancer Res* 2015;4(4):356-371. doi: 10.3978/j.issn.2218-676X.2015.08.03

Stereotactic body radiation therapy in lung

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Contributions: (I) Conception and design: SP. Giri; (II) Provision of study materials or patients: All authors; (III) Manuscript writing: All authors; (IV) Final approval of manuscript: All authors.

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Abstract: Lung cancer is the leading cause of cancer death worldwide, in both men and women. Contrary to the improved survival outcomes for many other types of cancers, the prognosis for people diagnosed with lung cancer remains poor, with 5-year relative survival ranging 6-18%. Majority of lung cancers diagnosed at locally advanced stage, due to the lack of observable symptoms for early stage lung cancer. Recently Lung Cancer screening in high-risk population with low dose CT scan showed 20% reduction in relative death from cancer. Screening allows diagnosing the cancer at early stage. For early (local only) stage, lobectomy is the treatment of choice that offers best 5-year overall survival of 60%. But majority of these patients are unable to tolerate the surgery due to poor pulmonary reserve or medical co morbidity. With the advent of new technology, improvements in imaging and treatment delivery enable us to extend the stereotactic radiation therapy to extra cranial sites. Stereotactic radiation therapy to lung reported 5-year local control rates in excess of 90% and overall survival of 40%. In this review article, we discussed the rationale, evidence supporting stereotactic body radiation therapy (SBRT) in lung tumors, radiobiology of hypofractionation, mediastinal staging, the treatment planning, and delivery process and also the role of SBRT in metastatic setting.

Keywords: Stereotactic body radiation therapy (SBRT); lung cancer; hypofractionation

Submitted Aug 20, 2015. Accepted for publication Aug 24, 2015.

doi: 10.3978/j.issn.2218-676X.2015.08.11

View this article at: <http://dx.doi.org/10.3978/j.issn.2218-676X.2015.08.11>

Introduction

Treatment of choice for stage I (T1-T2N0) non-small-cell lung cancer (NSCLC) is surgery. But many patients are unable to tolerate the resection due to poor pulmonary reserve or medically inoperable due to multiple comorbid conditions. Five-year overall survival for untreated patients with stage I NSCLC is 5% and median survival 9 months (13 months for T1), as reported by Raz *et al.* based on California cancer registry (1).

Primary radiation therapy is considered to be reasonable therapy, for non-surgical early-stage NSCLC with reported 5-year survival rates ranging from 10% to 30% (2).

A review of 156 medically inoperable patients with stage I NSCLC at Duke University between 1980 and 1995 demonstrated a 5-year, cause-specific survival rate of

32% with RT alone. Improved survival was significantly correlated with achieving local control and approached significance for higher RT doses (3).

The standard approach involves administering an approximate dose of 4,500 to 6,600 cGy in fractions of 180 to 200 cGy. Historically, RT fields for early-stage NSCLC encompassed the primary tumor and regional lymphatics in the ipsilateral hilum and mediastinum. This “prophylactic” treatment was based on the identified risk of occult nodal involvement from surgical series ranging up to 20%, and surgical data indicating better control with more extensive resections (4).

However, large RT fields are potentially poorly tolerated in this population of patients with limited pulmonary reserves. More recent retrospective experiences have demonstrated similar survival results with fields limited to

the primary tumor or gross disease alone, compared to fields including prophylactic treatment to lymph node chains (5,6).

Several studies reported safety and feasibility of dose escalation using 3D conformal radiation therapy to the gross disease alone omitting elective nodal irradiation was studied (7,8).

In a report from the Netherlands, limited “postage-stamp” fields were treated using hypo fractionated RT (i.e., 4,800 cGy in 400 cGy fractions) with reported 3-year overall and disease-specific survival rates of 42% and 76%, respectively (9).

The only dose finding study of stereotactic body radiation therapy (SBRT) for lung tumors was reported by Timmerman *et al.* from Indiana. They conducted a phase I study of dose escalation of a 3 fractions regimen, starting with 8 Gy \times 3, and escalating to 10, 12, 14, 16, 18, 20 and 22 Gy \times 3 fractions, in patients with potentially resectable NSCLC but who were not surgical candidates for medical reasons (“medically inoperable”). Doses were calculated without correction for tissue inhomogeneity. Patients were enrolled into three separate dose escalation groups based on tumor size. While dose-limiting toxicity (DLT) was observed in one or two patients at several dose levels, the protocol defined maximum tolerated dose (MTD) was only observed in patients with large T2 tumors (5-7 cm in size) at 22 Gy \times 3. In other tumor size groups, dose escalation was stopped prior to reaching the MTD (20-22 Gy \times 3). Greater than 90% primary tumor control was observed with 20 Gy \times 3; this total dose of 60 Gy corresponds to a biologically equivalent dose (BED) (if expressed in 2 Gy/fraction) of 180 Gy if using the formula $BED = nd (1 + d/\alpha/\beta)$, where n = number of fractions; d = dose per fraction; and $\alpha/\beta = 10$ for acute reacting tissue), although it is not clear how applicable this conversion is to highly hypofractionated treatments (10).

In a subsequent single institution phase II study of this SBRT regimen, Timmerman and colleagues treated 70 patients with early stage (T1-2, N0) inoperable NSCLC with 60 Gy in 3 fractions for T1 and 66 Gy in 3 fractions for T2.14 That study allowed enrollment of patients with tumors located anywhere within the lung, and confirmed high rates of primary tumor control: 95% at 2 years. After median follow up of 17.5 months, three patients demonstrated a local recurrence. The study was particularly instructive in terms of local toxicity: eight patients were deemed by the data safety monitoring board to have grade 3 or 4 adverse events resulting from SBRT; the adverse events were primarily respiratory (decline in pulmonary function, pneumonia, pleural effusion, apnea) and/or skin reaction;

they occurred a median of 7.6 months after completion of SBRT. Six patients may potentially have had grade 5 (i.e., fatal) toxicity. In five patients, these grade 5 adverse events were respiratory: one fatal hemoptysis (associated with a local recurrence) and four infectious pneumonias; the sixth patient died of complications from a pericardial effusion. These deaths occurred a median of 10.4 months after SBRT (range, 0.6-19.5 months). Tumor location was a strong predictor of toxicity, with hilar or pericentral tumors showing an 11-fold increased risk in grade 3-5 adverse events when compared to more peripheral tumors ($P=0.004$). Two-year freedom from severe adverse events was 54% for these central tumors, as compared to 83% for the peripheral tumors, defined as outside the “zone of the proximal bronchial tree”, which is a 2 cm radius around the main tracheo-bronchial tree: trachea; left and right main stem bronchi; right upper, middle, and lower lobe bronchus; and left upper, lingular, and lower lobe bronchus. The only other variable that was a predictor of toxicity, although not as strong as tumor location, was the size of gross tumor volume (GTV), with >10 cc tumors showing greater toxicity than smaller GTVs (11).

On the basis of these two studies, 60 Gy in 3 fractions was chosen as the dose for the RTOG-led phase II multicenter study, RTOG 0236, but patients with tumors within the above-described zone of proximal bronchial tree were excluded from the study. As in the prior phase I and II studies, the doses were calculated without correction for tissue inhomogeneity.

Five-year results of this study were presented at ASTRO 2014. In the of 55 evaluable patients, Primary recurrence was 7% (4/55), lobar recurrence 20% (9/55), loco-regional recurrence 38% (7/55-Nodal + adjacent organs), Disseminated failure entire lung: 31% (15/55). Disease free survival 26%, Overall survival 40% and Median survival were 4 years. Pulmonary toxicity observed was grade 3 in 27% (15/55), grade 4 in 3.6% (2/55) and no grade 5.

Radiobiology of SBRT

Radiation death is defined as loss of reproductive integrity of the cell when exposed to radiation. Traditionally it was explained by damage of DNA with radiation. Biologically effective dose (BED) based on the linear-quadratic (LQ) model is as follows:

$$BED = nd \times (1 - d/(\alpha/\beta))$$

In this calculation, n equals the number of fractions and

d equals the fraction size. The α component represents the linear portion of the cell survival curve, where a single radiation event (DNA double-strand break) causes cell death. The β component represents the quadratic portion of the cell survival curve, where cell death results from at least two double-strand breaks (12).

But at hypo fractionated regimens that were used in SBRT vascular effects due to endothelial apoptosis appears to play a major role. Endothelial cells upon exposure to high dose of radiation (>10 Gy) acid sphingomyelinase is translocated to the plasma membrane of endothelial cells where it plays a role in generating ceramide from sphingomyelin. Ceramide release leads to activation of the apoptotic protein BAX (13,14).

BAX is part of the Bcl-2 family of proteins and is important pro apoptotic regulator. Activation of BAX leads to the release of mitochondrial cytochrome c, which signifies commitment of the cell to apoptosis via intrinsic pathway (15). Endothelial apoptosis peaks within 6 hours after radiation and causes micro vascular dysfunction and hence acutely disrupts tumor perfusion (16).

SBRT in metastatic setting

Rusthoven *et al.*, studied patterns of failure after SBRT following first line systemic therapy for metastatic lung cancer. Local failure was noted in 64%, distant only failure was noted in 9% and in 14% failed both local and distant together. SBRT dose range was from 36-60 Gy in 3 fractions. Time to first progression was 3 months in local only failure compared to 5.7 months in distant failure (HR: 0.44; 95% CI: 0.22-0.90). This study suggests that SBRT could improve time to progression (17).

Another Ph II study by Iyengar *et al.*, treated metastatic NSCLC with <6 metastatic lesions with SBRT after early failure of systemic therapy. Failure rate was 6.4% in the SBRT treated lesions. Majority of patients progressed in new distant sites. Median progression free survival was 14.7 months and overall survival was 20.4 months, which exceeded the historical controls (18).

These initial studies proved the benefit of aggressive local treatment in the oligometastatic setting and safety of treating the metastases with SBRT when the lesions are at least 5 cm apart.

At present NRG-BR001 studying the safety of SBRT in treating multiple metastases particularly >3 or 2 lesions separated by less than 5 cm.

Mediastinal staging

Accurate mediastinal staging is essential for the treatment planning of SBRT patients with NSCLC to ensure they do not have lymph node metastasis. In addition to a traditional mediastinoscopy noninvasive methods have been developed. These include Computed tomography (CT) scans, FDG PET scan and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and endobronchial ultrasound-guided fine needle aspiration (EBUS-FNA).

CT provides an excellent anatomic detail in mediastinal staging of NSCLC. However, approximately 40% of nodes reported as malignant by CT criteria are benign, and 20% reported as benign prove to be malignant (19). In patients with clinical stage I tumors, 5% to 15% will have positive lymph nodes at surgery (20). Dwamena *et al.* in a metaanalysis showed an average CT sensitivity of 60% and specificity of 77% for the detection of mediastinal nodal metastases (21). In 2003, another meta-analysis by Toloza *et al.* reported the pooled sensitivity and specificity for CT at 57% and 82%, respectively (22). The 2007 American College of Chest Physicians (ACCP) Evidence-Based Practice Guidelines reported 51% pooled sensitivity and 85% pooled specificity (23). Hence CT falls short in its ability to accurately stage the mediastinum.

The major benefit of fluorodeoxyglucose-PET scans in the lung cancer is its ability to provide functional information during the evaluation for intrathoracic and extrathoracic metastases. Numerous studies have demonstrated a higher sensitivity and specificity for PET than CT in the detection of malignant mediastinal nodes, with various meta-analyses reporting PET sensitivities of 74% to 85% and specificities of 85% to 92% (24,25). A high negative predictive value (NPV) of >90% in nodal staging has also been reported (26). Normal physiologic uptake and artifacts can lead to false-positive (FP) results. The ability of PET to resolve small hypermetabolic abnormalities in nodes is limited (27). Takamochi *et al.* studied PET limitations in nodal staging in NSCLC and reported low spatial resolution as a major causative factor for their 20% False negative rate (28). PET also could not identify small tumor foci ranging from 1 to 7.5 mm. A Cochrane data base (29) review of 45 studies concluded that sensitivity and specificity estimates for PET-CT positivity criterion were 77.4% (95% CI: 65.3-86.1) and 90.1% (95% CI: 85.3-93.5), respectively. They concluded that PET CT alone could not be used in mediastinal staging of lung cancer. Thus current imaging advancements have not, however, supplanted invasive staging (30,31).

EUS-FNA is generally regarded as a safe procedure. Contraindications are few, and include inability to tolerate conscious sedation, esophageal obstruction, and uncorrectable blood dyscrasia. Complications are rare and usually minor (32). Lymph nodes as small as 4 to 6 mm can be detected by EUS as long as they are in the vicinity of the esophagus and not obscured by tracheal air or intervening blood vessels. A recent review of 2,756 patients demonstrated overall median sensitivity of 89% and NPV of 91% (19). A meta-analysis in 2008 by Puli *et al.* reported that FNA raised the sensitivity of EUS in the diagnosis of mediastinal adenopathy from 85% to 88% and the specificity from 85% to 96% (33). Prenzel *et al.* (34) reported that lymph node size was not a reliable predictor of metastatic involvement; 44% of metastatic lymph nodes in NSCLC patients studied measured <1 cm in short axis, 77% of patients without nodal metastases had a lymph node >1 cm, and 12% of patients with nodal metastases had no nodes >10 mm. Sonographic characteristics of lymph nodes identified during EUS have also been studied. Features reported as predictive of malignancy include rounded contour, sharply circumscribed border, hypoechoic echogenicity, and >1 cm diameter. An increased number of these features has been associated with a higher likelihood that a particular lymph node is malignant (80% to 100%), with 25% of malignant nodes reportedly fulfilling all four conditions (35,36). Kramer and Groen (37) published a meta-analysis of 14 studies in 2003 and reported the sensitivity of EUS-FNA as 81% to 97% and the specificity as 83% to 100% for the diagnosis of posterior mediastinal lymphadenopathy. In 2007, Micames *et al.* published a meta-analysis of 18 studies and reported a pooled sensitivity of 83% and specificity of 97% (32). EUS-FNA is therefore been recommended for staging of the mediastinum when CT and PET do not show disease. Mediastinoscopy should only be performed for patient with a high probability of having nodal disease and the EUS-FNA was negative for malignancy.

Practical aspects of planning SBRT

SBRT typically refers to a radiation therapy technique in which an extracranial tumor receives high doses (7-30 Gy) of radiation following a hypofractionated prescription of 5 or less fractions. Provision of these high doses while also achieving normal tissue doses less than tolerance is characterized by tight conformation of the prescription dose to the target volume, steep gradient fall-off away from the target edge,

and a high level of inhomogeneity of target dose. Due to the levels of conformity, inhomogeneity, and dose gradient fall-off, accurate tumor delineation, dose modeling, and treatment delivery are of extreme importance even compared to conventional intensity modulated radiation therapy (IMRT). These high standards of accuracy and precision for SBRT have led to much tighter tolerances when traditional QA tests are performed on treatment machines, treatment planning systems, and even patient plans, i.e., the guidance document published by the AAPM on QA of Linear accelerators where machines used to deliver SBRT are separated from those used for only conventional IMRT or 3D. In addition to the need for increased accuracy, proper and successful SBRT to the lung requires the consideration of another component which is delivery to a moving target. Consideration of the need for increased accuracy and breathing motion must occur at all steps in the radiation treatment planning and delivery process for SBRT Lung. What follows is a discussion of practical aspects of the aforementioned process (38-41).

Physics preparation

Prior to beginning a treatment technique, it must be commissioned by the physics staff. As small fields (i.e., <3 cm × 3 cm) techniques are to be used, this will likely include the acquisition of further beam data and characteristics that likely will not currently be included in the planning system. The treatment device used will need to be tuned and adjusted to meet stereotactic tolerances. Perhaps a totally new treatment device is to be used in which case this device (i.e., Cyberknife, Vero, ViewRay, etc.) will need to be commissioned for complete clinical use rather than simply for a given technique. Even among individual machines, accessories to be used in SBRT lung may differ such as stereotactic cones, multi-leaf collimator (MLC), or even micro-MLC and, therefore each must be commissioned before use. Motion management systems will also have to be tested and implemented properly. This work will require the physicist to be familiar with new and unconventional equipment even including the detectors used for data acquisition. The use of redundant equipment such as detectors is highly recommended so that clinical data obtained with each is corroborated by that obtained by the other (41,42). Proper procedures for this are extensive and require significant attention to detail, thus the full discussion of the topic is beyond the scope of this writing, however, SBRT commissioning processes have been described extensively in literature including a few American



Figure 1 Patient immobilized for 4D simulation utilizing a body-fix bag with evacuated plastic and a bellows belt for respiratory cycle capture.

Association of Physicists in Medicine (AAPM) task group (TG) reports. Recommendations from those guidance documents and others should be understood and followed (39,41-43).

Simulation

Simulation of a patient to be treated with SBRT to the Lung basically involves two parts:

- (I) Reproducible patient positioning and immobilization;
- (II) Proper acquisition of patient data (i.e., imaging).

Patient setup and immobilization

Patient setup and immobilization has come a long way since the introduction of 3D imaging and conventional IMRT. In order to provide consistent and reproducible setup, stereotactic body frames have been developed by a number of vendors. Many of the current generation of frames includes a fiducial-based localization system, however, most clinics avoid the use of such in body radiosurgery due to the availability of accurate image guidance and the inconsistency of tumor location in the body compared to coordinates based on external fiducials. These frames often consist of vacuum bags conformed to a large portion of the patient's body with the added option of active breathing management to be discussed later (44). Despite improvements in setup and immobilization for use in SBRT, the need for image guidance has been shown (*Figure 1*) (45,46).

Acquisition of patient data

Imaging and motion management

Technically, proper tumor diagnosis and/or biopsy is a major

part of this process; however, for the sake of this discussion, the focus will primarily be on the imaging portion of this step. Currently, CT is the modality of choice for treatment planning for lung SBRT. This is primarily due to the feasibility of reasonably accurate dose calculations based on the relationship of electron density and CT number which allows for proper consideration of tissue heterogeneity and radiation transport. All simulations of SBRT lung patients will utilize CT and then will take it a step further with the use of 4D CT. 4D CT combines the capture of a representation of the patient's breathing cycle with simultaneous CT imaging during the breathing motion. The patient breathing is graphed as a sinusoidal curve and during reconstruction the CT images are then organized based on the time point in the breathing cycle at which they were taken. Theoretically, each image would be mapped directly to the exact point in the respiratory cycle that it was taken and "binned" into a CT dataset with all other CT images scanned at that time point and each position. However, since there are infinite arbitrary time points in the cycle, the result would be CT datasets with limited numbers of images that would not represent the entire area scanned for all time points. For practical implementation, the respiratory cycle is divided into "phases" based on when in the cycle it occurs and each phase represents a range of time points in the cycle. Then, each CT image for a given slice position and given time point in a "phase" are sorted with all other CT images that occur at different slice positions but within the same "phase" of the respiratory cycle. Using the resulting datasets (typically 10 phases), one can hold the slice position constant, but rotate through the different phase datasets in order of their position in time on the respiratory cycle and the motion of the anatomy at that slice position should be represented as a "video". The aforementioned method represents phase binning and is the most commonly utilized 4D reconstruction method; however, amplitude binning is also an option utilized based on needs, raw data, and desired results. Also, typically, prospective binning is performed, but strategies exist for retrospective binning when desired results are not achieved by the latter (47-49).

Vendors provide different techniques for capturing the breathing cycle which utilize different forms of "surrogates" for respiration. Varian's RPM utilizes a camera system to watch external fiducials placed on the abdomen. The C-RAD Sentinel system implements a scanning laser over the abdominal surface. Philips interfaces with a bellows system around the abdomen that monitors air

flow dependent on the position of the abdominal surface. Even the Microsoft KINECT has been tested for use in the acquisition of the respiratory cycle. Regardless of the system utilized, the desired endpoint is the same and certain uncertainties exist which should be taken into account during the remaining treatment planning process. Some of these uncertainties have been described as inaccurate binning of CT images into their respective phase, non-correlation of a respiratory surrogate to actual tumor motion, and non-reproducibility of respiratory cycle throughout patient treatment. These uncertainties should be accounted for during the treatment planning and delivery process (40,50,51).

In addition to the 4D phase datasets, the data obtained from 4D scanning can also be reconstructed into intensity projection datasets. Maximum intensity projection (MIP) datasets are represented by each voxel being assigned its maximum CT number that occurred during the 4D cycle. Average intensity projection (Ave-IP) and minimum intensity projection (mini-IP) follow the same logic, but with the average and minimum CT numbers respectively. Theoretically representing the maximum tumor motion, the MIP comes into play as a useful single shot representation of the motion displayed by the 4D phases. The Ave-IP often comes into play when considering the optimal image for dose calculation. Mini-IP is not used very often in regards to lung, but does offer value in radiation with tumors in the abdomen, such as liver or pancreas (40,52-54).

Rather than simply acquiring the full potential tumor motion in an image, one may also take steps to actively reduce target motion before imaging it. Many types of active motion control exist with the simplest being to image during a breath hold at a particular time point in the respiratory cycle (typically full inspiration or full exhalation) with the intent of treating with this same breath hold status. A few systems have been designed that can assist the patient in reproducing the same breath hold each time while also communicating with the radiation oncology staff about the actual status of the patient's breathing. Another technique for motion reduction is to apply some type of abdominal compression. One form of this involves placing specially designed plastic wrap over the patient in their vacuum bag and then evacuating the air out from underneath it. A more rigid type of compression exists in the form of a frame that is placed over the patient's abdomen where a flat pad can be screwed down to apply pressure to the patient's upper abdomen until the desired tumor motion is achieved when reviewed with imaging. Another type of active

motion management is referred to as respiratory gating. Implementation of this technique will involve physician review of the 4D CT. He or she will decide which of the phases contain the target within an acceptable margin and the target delineation and treatment will be adjusted to only treat the outlined area during those chosen phases. Many have begun utilizing the placement of radiopaque fiducials in or near the tumor. This is typically done by the surgeon and usually greater than three days before the patient's scheduled radiation oncology simulation and assists in target identification and localization throughout the entire simulation and treatment process. Often, multiple types of motion management are used in tandem during the treatment process (40,41,43).

Imaging and target identification

In addition to motion management, one must consider the proper identification of the proposed target. Lung tumors, especially in the typical SBRT lung patient, can be shrouded by non-cancerous tissue that may obscure or even masquerade as the tumor itself. This can be especially problematic with tumors located near the diaphragm or in the presence of heavy atelectasis. The most common method of alleviating this issue is currently with the utilization of positron emission tomography (PET) often in conjunction with an anatomical CT (PET/CT). PET increases the specificity of imaging of malignant tissue and when fused with the planning images, can assist in accurate delineation of the tissues to be treated. Ideally, this PET image would be performed close to the simulation date and in the proposed treatment position to reduce the fusion uncertainty. This fusion can be performed rigidly or deformably using multiple types of software including most modern treatment planning systems (55,56). Another option to assist in target identification is the placement of radiopaque fiducials as mentioned above. The use of fiducials assists in target identification throughout the entire simulation and treatment delivery process (57,58).

Practical simulation considerations

As stated previously, the simulation should result in reproducible patient positioning and immobilization as well as proper acquisition of patient data for planning and treatment. For reproducibility, consideration should be given to items such as patient comfort, habitus, and mental status. Sometimes medication can be used to assist a patient in relaxation both at simulation and treatment. Ideally, a patient would be setup in such a manner so that pre-

treatment corrections could be maximally applied (robotic couches offer 6 degrees of correction and submillimeter corrections opposed to traditional treatment couches with only 3 degrees and subcentimeter corrections) however this may require a frame with infrared markers which will not fit over patients of a given habitus. Also, in some cases, the desired patient position may not be easily achievable due to patient's historical injuries or such and the simulation technique may need to be adapted. In general, though, patients should be positioned head first and supine with their arms up inside their immobilization device. CT imaging should achieve ≤ 3 mm slice thickness (one could optionally use variable slice thickness on some scanners to scan thin slices in and near the tumor and thicker as you get away from it) and should cover all normal tissues of interest as accurate dose volume histogram (DVH) data will be necessary on these structures. Margin well above and below the area to be treated will be necessary for accurate dose calculation and also due to the probable use of noncoplanar beam angles (39,40).

Patient data that is also of interest during SBRT lung planning is the clearance distance between the gantry and the patient when various gantry, collimator, and couch positions are utilized. The acquisition of this data is usually performed in three basic ways. The first method is to simply scan a larger portion of the patient during simulation so that collisions can be anticipated virtually and avoided. A second method is to take the patient and their immobilization devices to the treatment room after simulation and perform a comprehensive dry run positioning the gantry, couch, and collimator at various places with the patient aligned roughly at isocenter. The third method basically ignores this possibility (not completely as the planner still tries to avoid collision) and a treatment dry run is performed before the first fraction. If a collision is discovered, then the plan is quickly adaptively planned to avoid the collision but still achieve the planning goals.

Treatment planning

The treatment planning process, in general, includes several steps such as delineation of target and normal tissue volumes, determination of prescription and fractionation schedule, and calculation and optimization of the dose distribution. This process has several additional considerations (some discussed above) when compared to conventional fractionation or non-lung treatments. Several Radiation Therapy Oncology Group (RTOG) trials exist

that provide guidance and the opportunity for consistency in performance of the treatment planning process.

Contouring

Care should be taken to follow International Commission on Radiation Units (ICRU) and Measurements guidelines on the definition of target volumes. The GTV is delineated using a combination of what is visible on CT and PET, implanted fiducials, and clinical experience on one static CT image. For SBRT lung, the clinical target volume (CTV) is equal to the GTV. At this stage, the GTV is then expanded to the internal target volume (ITV) so that the ITV includes the GTV at all stages of the respiratory cycle. If the treatment utilizes respiratory gating, the ITV will only include the GTV on the phases to be included in the actual treatment delivery. Once the ITV has been created, it can then be expanded to create the planning target volume (PTV) using a geometrical expansion to account for setup uncertainty. RTOG protocols recommend a 5 mm expansion; however, one could justify a smaller number with high confidence in tumor localization. Normal tissues can be contoured according to RTOG guidelines. Typical evaluation structures for use during plan analysis are the body minus the PTV and the body minus the PTV with a 2 cm margin. A copy of the PTV may also be created to allow for volumetric control of the block margin around the PTV for better conformity (*Figure 2*) (59).

Dose prescription

This decision is made by the treating physician who may follow various protocols and guidelines that have been published. Typically, single fraction, high dose regimens are reserved for peripheral floating tumors that are "far" away from the mediastinum. Some people use the bronchial tree plus 2 cm in order to gauge whether a tumor is peripheral or central. Central lesions or those where rib fracture are a consideration are typically treated with more reserved fractionations in 3-5 fractions. Often when evaluating dose regimens, the LQ model can be used to calculate BED. Studies have shown that when $BED > 100$ Gy, local control and survival significantly improves. Further discussion of the LQ model and its use in SBRT lung can be found elsewhere. One should note that the indiscriminate use of this BED model is not recommended as the LQ model is an approximation and use with heavy hypo-fractionation is not yet verified and the need for improvements on the model

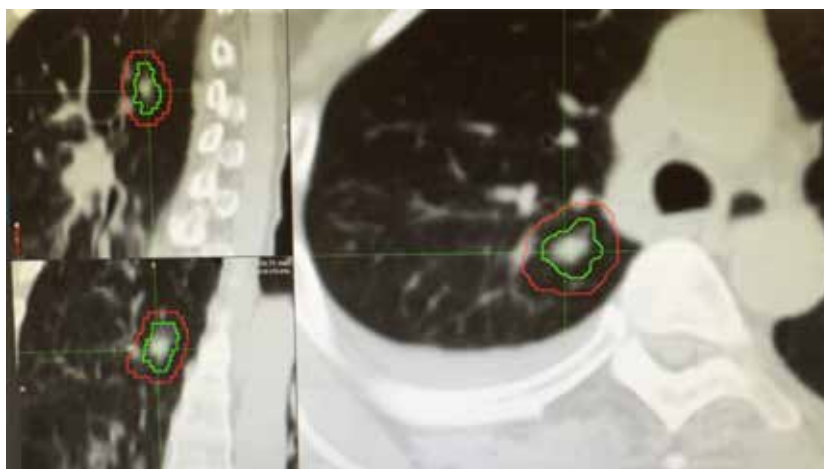


Figure 2 A three-view representation of the contours ITV (green) and PTV (red) for use in SBRT lung. The ITV was created by propagating the GTV contour from one phase of the respiratory cycle to all phases. The PTV was then created with a 5 mm expansion in all directions from the ITV. PTV, planning target volume; ITV, internal target volume; SBRT, stereotactic body radiation therapy; GTV, gross tumor volume.

for use with SBRT have been indicated by some (60-62).

Dose calculation and optimization

General

Regardless of technique, there are certain considerations during the dose calculation and optimization phase of the treatment planning process. Typically, one must be prepared to use multiple beams or arcs and also that these beams or arcs will need to approach the patient from a noncoplanar direction. Energy selection >6 MV is highly discouraged to avoid the excessive lateral scatter that occurs in a low density medium such as lung. Due to the high gradients (possibly about 10-12% per mm) expected and encountered in this type of plan, the dose calculation grid must be set with a high enough resolution that the distribution is accurately characterized. For the sake of efficiency, initial planning can be performed at a lower resolution before changing it for the final stages of dose calculation and optimization. Quantitatively, TG 101 of the AAPM recommends grid spacing of ≤ 2 mm and strongly discourage grid spacing >3 mm. In addition to grid spacing, an appropriate algorithm must be selected that correctly handles lateral electron scattering in addition to the presence of heterogeneities and their interfaces. Most consider convolution-superposition algorithms a necessity and recommend Monte Carlo when available. Though not universally applied, many institutions take precautions to avoid calculating dose to “normal” lung when the goal is to treat “solid” tumor. These methods

often include either using the Ave-IP for dose calculation or overriding the ITV to tissue density before dose calculation (39,40,52,53).

Regardless of planning technique, plans should be evaluated consistently using certain metrics. Typically, 100% of the prescription dose should cover 95% of the PTV and 90% of the prescription dose should cover 99% of the PTV ($D_{95} = 100\%$, $D_{99} = 90\%$). A conformity index should be used to ensure that only the PTV receives the prescription. Though inhomogeneity of dose is expected in SBRT lung, a homogeneity index should be used to govern that the level stays within a reasonable range such as that suggested by RTOG. A gradient index monitors that the desired gradient is achieved outside of the PTV to spare normal tissue. Various versions of these indices have been proposed. It should be noted that the values expected for the indices discussed above will differ depending on the exact treatment machine, accessories, and technique used in the treatment. The amount tissue outside of the PTV exposed to above prescription level dose should also be evaluated. Of course, dose to normal structures should also be evaluated. Constraints for all of the above have been listed in the various RTOG trial documents and mostly unvalidated normal tissue constraints have been published (*Table 1*) (63).

Prior to treatment of the patient on the machine and just as with any complex mode of radiation delivery, each patient’s treatment plan must undergo quality assurance on the treatment machine to ensure machine capabilities,

Table 1 Our departmental table used during SBRT evaluation to ensure we are meeting planning criteria for RTOG 0813 for 50 Gy in 5 fractions

Planning criteria	Goal values
Coverage	
$V_{90\%} \geq 99\%$	99%
$V_{100\%} \geq 95\%$	95%
Conformality	
$R_{100\%} \leq 1.2$	1.2
$R_{50\%}$	4.6
$R_{105\%}$ Outside of PTV $\leq 15\%$	15%
$D_{2\text{ cm}}$	2,588 cGy
Normal tissues (constraints per protocol)	
Spinal cord, max dose	3,000 cGy
Spinal cord, $V_{2,250\text{ cGy}} \leq 0.25\text{ cc}$	0.25 cc
Spinal cord, $V_{1,350\text{ Gy}} \leq 0.5\text{ cc}$	0.50 cc
Esophagus, max dose	5,250 cGy
Esophagus, $V_{2,750\text{ cGy}} \leq 5\text{ cc}$	5.00 cc
Ipsilateral brachial plexus, max dose	3,200 cGy
Ipsilateral brachial plexus, $V_{3,000\text{ cGy}} \leq 3\text{ cc}$	3.00 cc
Trachea and ipsilateral bronchus, max dose	5,250 cGy
Trachea and ipsilateral bronchus, $V_{1,800\text{ cGy}} \leq 4\text{ cc}$	4.00 cc
Great vessels, max dose	5,250 cGy
Great vessels, $V_{4,700\text{ cGy}} \leq 10\text{ cc}$	10 cc
Heart/pericardium, max dose	5,250 cGy
Heart/pericardium, $V_{3,200\text{ cGy}} \leq 15\text{ cc}$	15.00 cc
Whole lung-GTV, $V_{20\text{ Gy}} < 10\%$	10%
Whole lung-GTV, $V_{1,250\text{ cGy}} \leq 1,500\text{ cc}$	1,500 cc
Whole lung-GTV, $V_{1,350\text{ cGy}} \leq 1,000\text{ cc}$	1,000 cc
Skin, max dose	3,200 cGy
Skin, $V_{3,000\text{ cGy}} \leq 10\text{ cc}$	10.00 cc
Ribs, $V_{3,200\text{ cGy}} \leq 1\text{ cc}$ (RTOG 0915)	1.00 cc
Ribs, max dose (RTOG 0915)	4,000 cGy

SBRT, stereotactic body radiation therapy; PTV, planning target volume; GTV, gross tumor volume.

no dose calculation mistakes, and proper electronic transmission of treatment parameters to the treatment machine. Various methods of this process have been described and are offered by many different vendors. Physicists should put for significant effort to not only understand their QA devices and methods, but also to establish stringent enough tolerances for the pass or fail of each plan as typical tolerances for conventional IMRT

may not be acceptable. As with acquiring commissioning data, the use of multiple systems for corroboration is highly encouraged.

3D static fields

This technique is usually marked by 8-15 static fields directed at the PTV. Beams are arranged around the PTV in 20-40 gantry intervals typically avoiding the contralateral lung. A normalization point is placed at the center of mass of the PTV and the prescription is normalized to 60-90% at this point. With certain machines and accessories, it may be necessary to use more than 1 isocenter in order to achieve coverage or the technique may be nonisocentric in order to achieve coverage. Little or no block margin around the PTV is applied per RTOG protocols; however, best results are achieved when methods are utilized to create a variable margin around the PTV (if using MLC or non-static collimation such as cones). Typically, this means a positive margin of a few mm where the block edge intersects with a large amount of lung and a negative margin when the block edge may intersect or be near tissue density areas such as the chest wall or mediastinum. In some cases, the block may need to be adjusted to ensure that nearby normal tissues are appropriately spared. During plan optimization, multiple plan characteristics can be adjusted such as gantry, collimator, and couch positions, block margins, and prescription normalization percentage. Of course, what can be adjusted and how much is dependent on the machine and accessories in use.

3D conformal arcs

This technique involves one or more arcs during which either the isocenter is placed in the target so that the beam is always directed towards the target or the collimating device will direct the beam towards the target during the arc rotation. This technique is often optimized similarly to that of 3D static; however, it has certain tradeoffs when compared to it. It is often more difficult to achieve the same gradient with arcs, though the delivery time will be much shorter. In some cases, a hybrid plan involving 1-3 arcs and a noncoplanar static field or two will achieve planning objectives while sparing the efficiency (*Figure 3*).

IMRT static fields

Similarly to the relationship between conventional 3D and conventional IMRT, inverse optimization produces a treatment plan that meets the discussed goals potentially in a more efficient manner. Applied optimization objectives



Figure 3 An axial cut of a characteristic dose distribution for lung SBRT delivered using a linear accelerator and MLC via two coplanar arcs. SBRT, stereotactic body radiation therapy; MLC, multi-leaf collimator.

will be different with SBRT Lung as homogeneity within the PTV is not as important and a steep dose gradient is desired regardless of whether critical normal tissues are nearby. It should be mentioned that some institutions shy away from IMRT for SBRT lung due to the possibility of a large interplay effect within so few fractions. Some mitigate this issue with the use of gating and/or fiducial tracking. It should be noted that some studies have also found that this effect averages out over the total treatment, though the question remains whether the fractional dose is just as important as the total dose in SBRT lung. Regardless of feelings on the possible interplay effect, studies have shown that IMRT typically achieves better normal tissue sparing but less steep of a gradient when compared to 3D techniques and so may not be appropriate on a regular basis as this effect seems to magnify as target volumes become smaller (64-66).

VMAT

VMAT is the intensity modulated arc form of 3D conformal treatment and their relationship is similar to that described above between IMRT and 3D static fields. Interplay may still play a role in this delivery technique and similar results with normal tissue and dose gradient have been shown, therefore the same considerations for the use of VMAT in the lung should be taken into account (67-69).

Other delivery techniques

Depending on the equipment and device used, other techniques may be available that mimic any one of these

four mentioned above. Different delivery machines have different degrees of freedom and ability to adjust for target motion (70). CyberKnife with its possibly fiducial-less tumor tracking and nonisocentric delivery have become a popular method of lung SBRT (71,72). Even TomoTherapy units have been used for lung SBRT in many places as well (73,74). Other devices used are newer and are still being tested clinically by centers who have implemented those machines. It should be noted that recent emphasis has been placed on lung SBRT delivered with very high dose-rate. Due to the availability of linear accelerators without flattening filters, very high dose rates have become available and are being systematically employed in various centers around the world for lung SBRT treatment (75,76).

Treatment delivery

In today's image guidance age, treatment delivery consists of two parts:

- (I) Localization of target;
- (II) Radiation delivery.

Localization

The treatment delivery process begins with patient immobilization and setup just as it occurred during simulation. The treating therapists spend time to reproduce as closely as possible the setup that was acquired at simulation all the way down to exact vacuum pressure numbers and respiratory fiducial placement. Then, the patient is roughly aligned at the treatment isocenter based on external markings and imaging is performed. The imaging utilized can vary between sites; however, consistency typically exists for sites using similar machines for delivery. For traditional linear accelerators, cone-beam CT (CBCT) is the most common. However, relatively recently 4D CBCT has become available, but has not yet been adopted for widespread use even for SBRT lung. Fluoroscopy-based systems exist for traditional linear accelerators, but are most often utilized with other stereotactic machines. These systems are most useful when attempting to track tumor motion during delivery using implanted fiducials. Vendors are beginning to provide systems where the tumor can not only be tracked during delivery, but the collimating device or treatment couch can actually adjust to the actual tumor position. Currently, this "real-time" tracking requires the use of fiducials. Other systems may use megavoltage CT or even simplified magnetic resonance imaging. The latter is in development with current linear

accelerator vendors and would be ideal due to improved soft tissue contrast and zero imaging dose (39,40,43).

Regardless of the imaging technique utilized, imaging must occur prior to treatment and then the patient will be adjusted based on the comparison of the current image to reference images created during simulation and planning. The size of these shifts often dictates whether imaging should be performed again before treatment. In some departments, shifts >5 mm require a repeat CBCT before treatment to verify correct localization. Repeat imaging is also sometimes performed prior to adjusting couch rotation for noncoplanar beams and at the end of treatment. If respiratory gating is to be used, that system must be set up and synchronized with the delivery system before beam on. The same must also occur for any fiducial/tumor tracking systems.

Radiation delivery

Many departments require the presence of the physician and physicist during stereotactic hypofractionated procedures. Once the staff is present and pre-treatment setup and imaging is approved, treatment delivery can commence. It is important that all staff is aware of both the patient and the necessary monitoring systems. Any significant patient motion or system malfunction such as gating may require a pause in treatment and a repeat of setup and imaging. Treatments often take time on the order of 20-90 min from setup to delivery completion depending on staff familiarity, plan complexity or delivery technique, and delivery mechanism. The use of flattening filters in linear accelerators has been shown to significantly affect total delivery time (75,76).

Summary

SBRT to the lung requires great effort on the part of all the radiation oncology staff. Its success and not to mention convenience for the patient cannot be ignored. Each person involved must be sure to invest in the necessary attention to detail and consideration of challenges that SBRT lung requires. Even though its success in lung cancer has been shown, implementation and use of this technique carries with it a significant amount of risk for harm even when the procedure is performed properly (77).

Acknowledgements

None.

Footnote

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

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Cite this article as: Kanakamedala MR, Duggar N, Giri SP. Stereotactic body radiation therapy in lung. *Transl Cancer Res* 2015;4(4):435-448. doi: 10.3978/j.issn.2218-676X.2015.08.11

Brachytherapy in lung cancer: a review

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Abstract: Metastatic non-small cell lung cancer (NSCLC) remains the leading cause of cancer death worldwide. Intraluminal brachytherapy (ILBT) has been shown to improve patients' symptoms in some studies. However, its role in the palliation of these patients amidst the other local treatment modalities such as external beam radiotherapy (EBRT), laser and photodynamic therapy (PDT) remains unclear. We have completed a systematic review of the literature to evaluate outcomes of patients with lung cancer treated with ILBT alone and/or in combination with other treatment modalities. We have reviewed tumour and symptom response, overall survival (OS) and toxicities of patients treated with diverse fractionation schemes and those treated with a curative intent. Overall, ILBT is associated with improvement of patients' symptoms in most cases. Its toxicity profile is generally low with small risk of fatal hemoptysis. Further studies are needed to establish an optimal fractionation schedule, although it appears that fractionated treatments (3 fractions) were associated with less toxicity yet similar symptom relief when compared to single fraction treatments. Caution must be taken when prescribing the dose to avoid necrosis and or fistula that may be lead to fatal hemoptysis.

Keywords: Brachytherapy; lung cancer; non-small cell lung cancer (NSCLC); high-dose rate (HDR)

Submitted Aug 17, 2015. Accepted for publication Aug 17, 2015.

doi: 10.3978/j.issn.2218-676X.2015.08.08

View this article at: <http://dx.doi.org/10.3978/j.issn.2218-676X.2015.08.08>

Introduction

Metastatic non-small cell lung cancer (NSCLC) remains the leading cause of cancer death in men and the second leading cause of cancer deaths in women worldwide (1). It is a debilitating disease that results in a high burden of symptoms including shortness of breath, hemoptysis, cough and pain resulting in poor quality of life. Intraluminal brachytherapy (ILBT) has been shown to improve patients' symptoms in some studies. However, its role in the palliation of these patients amidst the other local treatment modalities such as external beam radiotherapy (EBRT), laser and photodynamic therapy (PDT) remains unclear. Effectiveness in palliation and toxicity profile vary widely between cohorts of patients treated with different fractionation schemes making it difficult to compare them.

Finally, ILBT has also been used in different ways to treat patients in a radical setting in small series.

We have endeavoured to pursue a systematic review of the literature to evaluate outcomes of patients with lung tumours treated with ILBT alone and/or in combination with other treatment modalities. We have reviewed outcomes of patients treated with diverse fractionation schemes and those treated with a curative intent.

Methods and materials

Literature search

The English and French-language literature from 1980 to June 1st 2015 was reviewed according to PRISMA guidelines (2), using PubMed. All relevant abstracts and

articles were thoroughly examined by two independent individuals. Studies were included if they (I) consisted of randomized control trials (RCT), prospective studies or retrospective studies; (II) included patients with biopsy-proven lung cancer and treated with ILBT.

Studies were excluded if they (I) included patients treated for distant lung metastases (II) were non-original studies, i.e., practice guidelines, metaanalyses or systematic review articles (III) did not address patients' outcomes after treatments of their endoluminal lung cancer; (IV) included patients treated with interstitial brachytherapy; (V) patients were treated post-operatively; (VI) treated patients with low-dose rate brachytherapy (LDR), medium dose rate brachytherapy (MDR) or pulse-dose rate brachytherapy (PDR).

The results were divided into into RCTs, prospective studies and retrospective studies. Although meta-analyses, systematic reviews and practice guidelines were not included in our literature search, these were cross-referenced with our search strategies to ensure a complete set of manuscripts for review. The following keywords and MeSH headings were used: "radiotherapy or irradiation or external beam or radiation" and "palliation or palliative or lung cancer or bronchial or endobronchial or lung malignancy" and "thoracic cancer or lung cancer or bronch- or endobronchial" and "palliation or palliative or lung cancer or bronchial or endobronchial or lung malignancy".

Results

Randomized control trials describing the role of ILBT alone or in conjunction with other modalities in the palliative management of lung cancer

ILBT allows the delivery of high-dose radiation to the luminal aspect of the tumour and thereby, relieving patients' symptoms. Few RCTs have attempted to assess the benefit of ILBT in addition to or compared to other treatment modalities, with conflicting results. These are studies with their results are summarized in *Table 1*.

Many RCT have randomized patients to EBRT with or without ILBT to evaluate the impact on outcomes with the addition of ILBT.

Huber *et al.* (8) randomized 93 patients with NSCLC treated with ILBT to a mean delivered dose of 13.4 Gy in 4 weekly fractions or 13.7 Gy in 2 fractions over 3 weeks. The 1-year survival, local control (LC) and fatal hemoptysis rates were not significantly different between the two

groups. Huber *et al.* (7) also randomized 98 patients with inoperable NSCLC to EBRT alone (n=42) compared to EBRT with ILBT (EBRT-ILBT) (n=56). In this trial, although survival rates (and fatal hemoptysis rates) were similar, patients with primary lung squamous cell carcinoma experienced a significantly longer LC when treated with EBRT+ ILBT compared to EBRT alone.

More recently, Langendijk *et al.* (4) randomized previously untreated NSCLC stage I-IIIB in proximal airways to EBRT to 30 Gy in 10 fractions with or without ILBT to a dose of 15 Gy in 2 fractions delivered weekly. This study showed that the addition of ILBT to EBRT improved the rates of re-expansion of collapsed lung from obstructing tumours in the main bronchus resulting in lower levels of dyspnea. There were improved rates of re-aeration (57% vs. 35%, P=0.001) and mean dyspnea scores (P=0.02) over time in patients treated with EBRT-ILBT compared to those treated with EBRT alone.

Stout *et al.* (6) randomized 99 patients with inoperable NSCLC to EBRT (30 Gy over 10-12 days) or ILBT (15 Gy). Although patients treated with EBRT had significantly longer survival (9.4 vs. 8.2 months), their dysphagia rates were also higher. ILBT and EBRT both provided similar symptom response rates. Of note, in this study, many patients treated with EBRT also received ILBT and vice versa. Patients' tumour size response was not reported.

Niemoeller *et al.* (3) randomized 142 patients with advanced endoluminal centrally located malignant tumours to a different ILBT fractionation schemes, i.e., 15.2 Gy in 4 weekly fractions (n=60) or 14.4 Gy in 2 fractions in 3 weeks. In both groups, survival and symptom response were similar. Interestingly, local tumour response with 2 fractions was significantly higher compared to 4 fractions (median 12 vs. 6 weeks, P<0.015) and fatal hemoptysis rate was lower (12% vs. 18%), although it did not reach statistical significance. Niemoeller *et al.* attributed the difference in the results to a higher radiation dose per fraction. It is also possible that the larger sample size of Niemoeller's cohort and the difference in the randomization method—performance status in each group was not described and not accounted for—may explain these different findings.

Chella *et al.* (5) evaluated the role of ILBT in addition to Nd-YAG laser in a RCT. Their study included 29 patients with NSCLC involving the central airways between Nd-YAG versus Nd-YAG with ILBT. The addition of ILBT to Nd-YAG increased the symptom-free survival (8.5 vs. 2.8 months P<0.05) and decreased the need of further

Table 1 Randomized control trials evaluating outcomes of patients with lung cancer treated with intraluminal brachytherapy

Author, year	Population	N	Treatment	Median follow-up	OS median/1-year OS (%)	Sympt resp (%)	Tumour resp (%)	A/E
Niermoeller et al., 2013 (3)	Endobronchial central NSCLC tumours	Total=142 (I) n= 60 (II) n=82	(I) 3.8 Gy q1wk x 4# (15.2 Gy) @ 1 cm (II) 7.2 Gy x 2# (14.4 Gy) @ 1 cm	20 mos	19 wks/ median 1-yr OS: 11% 18 wks/ median 1-yr OS: 21% (ns)	NR	49% 53%	fHemop: 18% fHemop: 12% (ns)
Langendijk et al., 2001 (4)	Inoperable, biopsy-proven NSCLC with tumor in main or lobar bronchus, Stages I-IIIb (IIb 55%)	Total=95 (I) 47	(I) EBRT alone Radical EBRT: 2.25 Gy x 4# q1wk to 45 Gy + 15 Gy boost, or palliative EBRT: 3 Gy x 4# q1wk to 30 Gy (II) EBRT+BT Radical or palliative EBRT + BT of 7.5 Gy x 2# @ 1 cm q1wk	NR	8.5 mos/NR (95% Ci: 5.4-11.6)	*SOB: 37% *Re-aeration: 35% Hemop 82%	NR	fHemop: 13%
Chella et al., 2000 (5)	NSCLC involving central airway not eligible for other treatments (Sq 72%)	Total=29 (I) n=15 (II) n=14	Nd-YAG laser alone: 25-45 Watts using pulses up to 1.2 s to a mean total of 1,850 J Nd-YAG laser + BT (15 Gy/3# q1wk @ 0.5 cm)	17.8 mo	7.0 mos/NR (95% Ci: 5.3-8.9) P=0.21 7.4 mos/NR	*SOB: 46% *Re-aeration: 57% Hemop: 86%	NR CR: 66%	fHemop: 15% Fistula: 4% n=5 (gr2 actinic bronchitis) n=1 (gr 3 actinic bronchitis- dilatation required) fHemop: 0
Stout et al., 2000 (6)	Inoperable, histologically proven NSCLC, Sq 82%	n=99 (I) 50 (II) 49	EBRT: 30 Gy/8# over 10-12 days BT: 15 Gy /1# @ 1 cm	NR	9.4 mos/88% 8.2 mos/22% (P=0.04)	67% cough (ns) 50% cough (ns)	NR NR	Massive hemop: 8% Massive hemop: 6% less dysphagia than EBRT
Huber et al., 1997 (7)	Inoperable, histologically proven NSCLC (Sq 69%, Stages I-IV (IIIb/IV 77%))	Total n=98 Group 1: n=42 Group 2: n=56	EBRT alone: 2-2.5 Gy/d with 4-5# /wk up to 50 Gy + 10 Gy boost (60 Gy total) Mean= 50.5 Gy EBRT + BT: BT: 4.8 Gy x 2# (1 wk pre- and 3 wk post-EBRT) @ 1 cm; mean BT: 7.44±2.6 Gy; mean EBRT =50 Gy	30 mos	6.5 mos/19% 6.2 mos/25% (ns)	NR	NR	fHemop: 14% fHemop: 19% (P=0.53) longer LC, *SCC

Table 1 (continued)

Table 1 (continued)

Author, year	Population	N	Treatment	Median follow-up	OS median/1-year OS (%)	Sympt resp (%)	Tumour resp (%)	A/E
Huber <i>et al.</i> , 1995 (8)	Histologically proven NSCLC (ns), Sq 49%, Stages I-IV (IIIB/IV 80%)	Total: n=93 Group 1: n=44	BT: 3.8 Gy x 4# q1wk @ 1 cm (mean dose: 13.4±5.2 Gy)	30 mos	4.2 mos/11.4%	NR	CR: 2% PR: 42%	NR
		Group 2: n=49	BT: 7.2 Gy x 2# q3wk @ 1 cm (mean dose: 13.7±4.4 Gy)		4.4 mos/20.4% (ns)		PR: 49%	

A/E, adverse events; BT, brachytherapy; CI, confidence interval; CRT, chemoradiation; EBRT, external beam radiation; Gy, Gray; mo(s), month(s); fHemop, fatal hemoptysis; Hemop, hemoptysis; n, number of patients; NR, not reported; NS, not significant; NSCLC, non-small cell lung cancer; q, every; OS, overall survival; resp, response; Rx, treatment; SOB, shortness of breath; Sq, squamous cell carcinoma; symp, symptom; wk(s), week(s); *, statistically significant; #, fraction(s).

endoscopic treatments (15 *vs.* 3 further endoscopic treatments, $P < 0.05$). It is possible that these two treatments are in fact complimentary. Indeed, Nd-YAG laser may be used to remove bulky tumours-to relieve symptoms rapidly while delivering ILBT provides a longer symptom-free survival and limit the needs of further interventions.

The current data suggests that in patients with endobronchial disease, ILBT given in addition to EBRT may improve LC and symptoms, especially in patients with collapse lung. When ILBT is delivered without EBRT, the use of Nd-YAG laser may be complimentary because it can remove bulky tumours and relieve symptoms rapidly and while ILBT provides a longer period of symptom-free survival. Further studies are needed to better evaluate and quantify the benefits of the addition of ILBT to EBRT in a palliative setting.

Prospective studies describing the role of ILBT alone or in conjunction with other modalities in the palliative management of lung cancer

Ornadel *et al.* (9) reported outcomes of 117 patients previously treated patients undergoing with Nd-YAG laser prior to BT if there was significant endobronchial likely to cause lung collapse before ILBT would have time to relieve obstruction or if patients were in acute distress. ILBT dose was of 15 Gy in 1 fraction, prescribed at 1 cm from the source axis. There was an improvement in symptoms in 59% for cough, 50% for dyspnea and 76% for hemoptysis. Of note, patients with prior laser treatments had a statistically significantly higher risk of subsequent fatal hemoptysis.

Muto *et al.* (10) reported outcomes of 320 patients with stage III NSCLC treated with EBRT (60 Gy in 30 fractions) and with three different schedules of ILBT of 10 Gy in 1 fraction, 14 Gy in 2 fractions and 15 Gy in 3 fractions. The mean OS and rates of symptomatic improvements were not statistically significantly different between the groups. However, the group treated with 3 fractions experienced less toxicity.

Skowronek *et al.* (11) treated 15 patients with 20-30 Gy of EBRT and a weekly high-dose rate (HDR) brachytherapy (3 fractions of 3.5-10 Gy, at 1 cm from the source). In all patients subjective improvement (regression of all symptoms) was found on the first check-up following treatment. In one case complete remission of the tumour lasted for over 6 months, 9 cases had partial remission. The combination of ILBT and EBRT led to regression of

symptoms and improvement of well-being in most patients.

Speiser *et al.* (12) reported one of the largest series of patients treated with ILBT with or without EBRT. The ILBT dose ranged between 22.5 and 30 Gy in 3 fractions. There was a high symptom response rate ranging between 85% (cough, SOB) and 99% (hemoptysis). The rates of procedure-related complications were low, at 3%.

Finally, Freitag *et al.* (13) assessed indirectly whether PDT compared to PDT with ILBT improved tumour response. This prospective study included unresectable endobronchial primary bronchogenic carcinoma (n=15) and recurrent lung tumours (n=17). The complete response rate associated with the initial PDT was of 75%. After patient completed ILBT, the CR was of 97%. These results suggest that perhaps delivering ILBT in addition to PDT may improve tumour control. It would be interesting to evaluate how ILBT alone compares to PDT, with the hope of using only one modality of treatment and minimize toxicities.

Most recently, Goldberg *et al.* (14) reported outcomes of inoperable patients with endobronchial lung cancer treated with ILBT with or without EBRT or chemoradiation. ILBT was delivered with a dose of 14 Gy in 2 fractions. Although the survival was improved in patients with CRT, the mean cough-free survival (4.7 months), mean shortness of breath-free survival (5.8 months) and hemoptysis free-survival (7.7 months) were not statistically significant between groups.

Freitag *et al.* (13) assessed indirectly whether PDT compared to PDT with ILBT improved tumour response. This prospective study included unresectable endobronchial primary bronchogenic carcinoma (n=15) and recurrent lung tumours (n=17). The complete response rate associated with the initial PDT was of 75%. After patient completed ILBT, the CR was of 97%. These results suggest that perhaps delivering ILBT in addition to PDT may improve tumour control. It would be interesting to evaluate how ILBT alone compares to PDT, with the hope of using only one modality of treatment and minimize toxicities.

All these prospective studies used different fractionation schemes and doses. All series report a good rate of symptom relief with low incidence of toxicities. Further studies are needed to determine the optimal dose fractionation scheme.

Retrospective studies describing the role of ILBT alone or in conjunction with other modalities in the palliative management of lung cancer

Many fractionation schemes have been described in

retrospective series. The vast majority of the literature on ILBT discusses its use in the palliation of patients with lung cancers to relieve symptoms such as hemoptysis, cough, dyspnea or atelectasis. The data is summarized in *Tables 1-3*. Its effectiveness in improving symptoms mostly ranges from 43% to 92%, depending on symptoms evaluated. Hemoptysis is the most consistently and effectively palliated symptom, with relief in 70-100% of cases. On the other hand, dyspnea is the symptom the least consistently relieved, with rates ranging from 33-85%.

Technical aspect of ILBT

Prescription point

The prescription point for lung brachytherapy is usually 1 cm from the centre of the source axis. Many authors attempt to treat the entire tumor with the brachytherapy catheters. For tumours in the trachea and mainstem, a prescription point at 1cm from the centre of the source axis is safe. From Goldberg *et al.* experience (18), it appears that prescribing at a depth of 0.5 cm was associated with no toxicities. It is not always possible to treat the entire tumour. Dose prescription points beyond what is recommended above can lead to massive cartilage necrosis causing airway-vascular fistula and massive haemoptysis.

Optimal dose fractionation scheme for palliative endobronchial brachytherapy for patients with lung cancer

In a palliative setting, the ideal treatment schedule aims to balance maximal LC and tumour and symptom response with minimal toxicities from ILBT (such as fatal hemoptysis), number of treatments and overall treatment time. There are innumerable fractionation schemes published in the literature with limited studies comparing them to establish superiority of one over the others.

Huber *et al.* (8) randomized 93 patients with NSCLC to a mean delivered dose of 13.4 Gy in 4 weekly fractions or 13.7 Gy in 2 fractions q3weeks. The 1-year survival, LC and fatal hemoptysis rates were not significantly different between the two groups.

One of the largest study from Niemoeller *et al.* (3) randomized 142 patients with advanced endoluminal centrally located malignant tumors to two fractionation schemes, i.e., 15.2 Gy in 4 weekly fractions (n=60) or 14.4 Gy in 2 fractions over 3 weeks. In both groups, survival and symptom responses were similar. Interestingly, local tumour response with 2 fractions was significantly higher compared to 4 fractions (median 12 *vs.* 6 weeks, P<0.015)

Table 2 Prospective studies evaluating outcomes of patients with lung cancer treated with intraluminal brachytherapy

Author, year	n	Population	Treatment	Symptomatic response (%)	Size response (%)	FU time	OS (mos)	Toxicity
Goldberg et al., 2015 (14)	98	Inoperable endobronchial lung cancer	n=52- BT alone: 7 Gy x 2# n=34- BT 7 Gy x 2# + EBRT (30 Gy/10#) n=6- BT 7 Gy x 2# + CRT (60 Gy/30#) n=6- BT 7 Gy x 2# + Chemo alone @ 1 cm for main and 0.5 cm for segmental bronchi	Mean cough-free survival = 4.7 mos Mean SOB-free survival =5.8 mos Mean Hemop-free survival =7.7 mos (ns) *no difference in sympt-free survival or QOL between treatment groups	NR	12 mos	Mean =4.6 mos Mean =7.5 mos Mean =10.5 mos* Mean =8.4 mos	NR
Skowronek et al., 2009 (11)	648	Advanced lung cancer	n=303- BT: 22.5 Gy/3# @ 1 cm q1wk n=345- BT: 10 Gy/1# @ 1 cm	88% (subsidence of all symptoms at 4 weeks post-ILBT)	CR: 17% PR: 71%	NR	Median = 3.7 mos (ns)	NR
de Aquino et al., 2013 (15)	78	Primary or metastatic bronchogenic carcinoma	BT (22.5 Gy/3#) + EBRT (60 Gy/30# or 30 Gy/10#)	Overall: 87% Cough: 34% SOB: 57% Hemop: 100% AO: 74% Infection: 80%	CR: 48%	NR	Median =6 mos	Stenosis-stent: 1.3% Fistula 2.6% fHemop 10% (but with PD)
Freitag et al., 2004 (13)	32	unresectable endobronchial primary bronchogenic carcinoma (n=15) and recurrent lung cancer (n=17)	PDT + BT (20 Gy/5# @ 1 cm)	NR	CR: 75% (after PDT) CR: 97% after PDT+ BT	Mean =24 mos	NR	No A/E ≥ grade 3 A/E
Escobar-Sacristan et al., 2004 (16)	81	Primary or metastatic endobronchial cancer	BT: 5 Gy @ 0.5-1 cm +/- surgery, chemo, CRT, laser or EBRT	Overall: 85% Cough: 88%, SOB: 75%, hemop 96%	CR: 57% PR: 41%	Minimum 1 month after BT	NR	Fistula (1%)-no mediastinitis/death
Muto et al., 2000 (10)	320	Biopsy proven NSCLC, KPS >60, Stages IIIA-IIIIB	EBRT (60 Gy/30#) + BT (3 schedules of BT) (i) 10 Gy/1# (ii) 14 Gy/2# (iii) 15 Gy/3# @1 cm (iii) 15 Gy/3# @0.5 cm	Cough: 77%, SOB: 85% Hemop: 94%, atelectasis: 94% Obstructive pneumonia: 90%	NR	5-36 mos	Mean =9.7 mos (ns between groups)	ACUTE: 6-mo bronchitis 16-80% (ss) CHRONIC: Fhem: 2.5-6.5% fistula 1-3% 3# associated with fewer A/E but similar OS and sympt relief; trend in higher A/E in C1 vs. C2

Table 2 (continued)

Table 2 (continued)

Author, year	n	Population	Treatment	Symptomatic response (%)	Size response (%)	FU time	OS (mos)	Toxicity
Ofiara et al., 1997 (17)	24	Bronchogenic carcinoma inoperable, recurrent or persistent symptomatic	24 Gy/3# @ 1 cm	Cough: 46% SOB: 33% Hemop: 79% Atelectasis: 54%	62%	NR	NR	NR
Ornadel et al., 1997 (9)	117	Bronchial carcinoma unresectable and not candidate for EBRT	BT: 15 Gy/1# @ 1 cm	Cough: 59% SOB: 50% Hemop: 76%	NR	NR	Median =12 mos	*Prior laser has higher risk of fHemop (P=0.048)
Hernandez et al., 1996 (18)	26	Residual or recurrent lung cancer	Prior EBRT (mean =44 Gy) BT: 7.5-10 Gy x 1-3# (total=7.5-30 Gy) @ 1 cm	Atelectasis 44% Hemop 71% Cough 55% SOB 36% Pneumonitis 50%	42%	NR	NR	n=6/29 (minor hemoptysis <100 mL) n=1/29: (non fatal massive hemop >500 mL) n=1/29: PTx
Trédaniel et al., 1994 (19)	51	Primary carcinoma of tracheobronchial tree	BT alone (14-21 Gy/2-3#) (I) BT radical (n=29) (II) metastatic: BT palliative (n=22)	Overall: 70% Cough: 85% SOB: 55% Hemop: 85%	Group 1: CR: 84% PR: 12% Group 2: CR: 27% PR: 59%	NR	Mean OS (I) 23 mos (II) 5 mos	Abscess: 4% fHemop: 10%
Goldman et al., 1993 (20)	20	Carcinoma in the bronchus	BT alone: 15 Gy/1# @ 1 cm	SOB: 89% (17/19) Cough: 37% (7/19) Hemop: 100% (6/6) Collapse: 69% (9/13)	CR: 42% PR: 47%	NR	NR	NR
Speiser et al., 1993 (12)	(Total: 342) 47	Curative	(I) EBRT (60 Gy/30#) + IDR (30 Gy/3#)	SOB: 86% Pneumonia: 86% Hemop: 99% Cough: 85%	NR	NR	NR	3% procedure-complications 7.3% fHemop
	144	Palliative	(II) EBRT (37.5Gy/15#) + HDR (30 Gy/3#)					
	151	Recurrent	(III) HDR (22.5 Gy/3#) @ 1 cm					
Bedwinek et al., 1992 (21)	45	Recurrent endobronchial carcinoma	6 Gy/1# @ 1 cm	Overall: 76% (29/38) Cough and hemoptysis: 80% SOB: 71% Atelectasis: 64%	CR: 41% PR: 41%	2-12 mos	Median =6.5 mos	fHemop: 32%
Gauwitz et al., 1992 (22)	24	Recurrent endobronchial cancers	9 Gy/1# @ 1 cm	Overall: 88% (21/24) Reoperation: 83% (15/18)	100%	NR	NR	n=1 min hemop n=1 fHemop

Table 2 (continued)

Table 2 (continued)

Author, year	n	Population	Treatment	Symptomatic response (%)	Size response (%)	FU time	OS (mos)	Toxicity
Mehta <i>et al.</i> , 1992 (23)	66	Endobronchial tumours	(I) LDR: 32 Gy/4# BID x 2 days @ 1 cm (II) HDR: 20 Gy/4# BID x 2 days	Overall: 78% Cough: 68%; SOB: 79%; Pneumonia: 82%; hemop 91%; Chest pain: 73%	78%	Median 6.5 mos	Median =5.5 mos; 1-yr 1%	Fistula 11%
Sutedja <i>et al.</i> , 1992 (24)	31	Recurrent endobronchial stage III lung cancer	10 Gy/1# @ 1 cm	SOB: 82% (18/22)	PR: 72%	NR	PR: 7 mos NR: 3 mos	fHemop 33% Fistula 10%
Burt <i>et al.</i> , 1990 (25)	50	Inoperable symptomatic endobronchial carcinoma	BT alone (15-20 Gy/1#) @ 1 cm (n=1 had EBRT, n=1 had chemo also)	Cough: 50%, SOB: 64%, Hemop: 86%, atelectasis: 33%	88% (15/17)	NR	NR	Asymptomatic PTX (n=1)

A/E, adverse events; BID, twice a day; BT, brachytherapy; chemo, chemotherapy; CI, confidence interval; CRT, chemoradiation; EBRT, external beam radiation; Gy, Gray; mo(s), month(s); fHemop, fatal hemoptysis; n, number of patients; HDR, high-dose rate brachytherapy; Hemop, hemoptysis; KPS, Karnofsky performance status; LDR, low-dose rate brachytherapy; NR, not reported; NS, not significant; NSCLC, non-small cell lung cancer; q, every; OS, overall survival; PD, progression of disease; PDT, photodynamic therapy; PTX, pneumothorax; resp, response; Rx, treatment; SOB, shortness of breath; Sq, squamous cell carcinoma; symp, symptom; wk(s), week(s); *, statistically significant; #, fraction(s); †, among evaluated patients.

Table 3 Retrospective studies evaluating outcomes of patients with lung cancer treated with intraluminal brachytherapy

Author, year	Disease description	N	HDRE/EBR treatment	Median FU (mos)	Med OS (mos)	Toxicity hemoptysis (%)	Toxicity (%)	Turnour resp (%)	Symptom response (%)
Rochet <i>et al.</i> , 2013 (26)	NSCLC inoperable stage I-III ineligibile Sx/Chemo	35	EBRT (50 Gy) + BT (15 Gy/3#)	26	NR	fHemop (3%)	Hemoptysis (6%), necrosis (3%)	PR (17%); CR (57%)	NR
Chan <i>et al.</i> , 2011 (27)	Early-stage inoperable NSCLC -> RFA+BT	17	Median 18 Gy/1# (14.4-20 Gy)	22 mos	21/2-yr OS: 53%	NR	PneumoTx (11/17) empyema (1/17) pleural effusion (3/17)	NR	NR
Zaric <i>et al.</i> , 2010 (28)	NSCLC	761	14 Gy/2#	NR	NR	1.1%	5% overall acute A/E; severe hypoxemia (1.7%)	NR	NR
Dagnault <i>et al.</i> , 2010 (29)	Iry and metastatic endobronchial tumours <6 mos survival	81	5 Gy x 4# =20 Gy	NR	14.7	1% (gr 1)	46% bronchitis gr1	60% pCR 42% radial resp	SOB: 85% Hemop: 100% Cough: 77%
Skowronek <i>et al.</i> , 2009 (11)	Advanced endobronchial NSCLC non-curative dz, treated with HDR alone	648	(I) 22.5/3# q1wk (n=303) (II) 10 Gy/1# (n=345)	NR	3.71 mos	NR	NR	CR: 17% PR: 71%	15% at 1 yr
Fortunato <i>et al.</i> , 2009 (30)	Primary and recurrent bronchial tree tumour treated with BT, EBRT, chemo, laser	7	EBRT (30-44 Gy) + BT (5-7 Gy/2-4#)	Mean 17 mos	Mean 54 mos	n=1 (14%) fHemop	Fatal hemoptysis 6 mos post-BT due to necrosis of bronchial wall due to PD n=1- grade 1 dysphagia	6/7 (86%)	6/7 (86%) at 72 h
Ozkok <i>et al.</i> , 2008 (31)	NSCLC st III and palliative patients	Total: 158 n=43	@ 1 cm (I) NSCLC III: EBRT (60 Gy/30#) + BT (15 Gy/3#) @ 1 cm	NR	Median OS: 11 mos CR: 15 mos NR: 9 mos (P=0.03)	fHemop 4%	Fibrous tracheal malacia (n=1) esophagitis gr 3 (n=3) bronchitis (n=6) (P=0.03)	86%	Cough: 58% SOB: 77% Hemop: 100%
		n=74	(II) EBRT (30 Gy/10#) + BT (15 Gy/2#) @ 1 cm			fHemop 11%	Fibrous tracheal malacia (n=1) bronchitis (n=1)	77%	Cough: 57% SOB: 90% Hemop: 94%
		n=41	(III) recurrent: BT (22.5 Gy/3#) @ 1 cm			fHemop 20%	Bronchitis (n=1)	72%	Cough: 55% SOB: 78% Hemop: 77%
Kubaszewska <i>et al.</i> , 2008 (32)	NSCLC + SCLC	270	8-10 Gy/1#, 22.5/3#	NR	NR	NR	NR	80%	Cough: 77% SOB: 76% Hemop: 92% Pneumonia: 82% Re-aeration: 73%

Table 3 (continued)

Table 3 (continued)

Author, year	Disease description	N	HDRE/EBR treatment	Median FU (mos)	Med OS (mos)	Toxicity hemoptysis (%)	Toxicity (%)	Tumour resp (%)	Symptom response (%)
Zorlu <i>et al.</i> , 2008 (33)	Recurrent endoluminal NSCLC	21	Palliative EBRT then BT (10 Gy/1# (n=9) and 15 Gy/1# (n=12) @ 1 cm	NR	5.5 mo (range, 4-12 mo)	fHemop 5%	Intrabronchial edema (5%)	NR	SOB: 71% Hemop: 80%
Mallick <i>et al.</i> , 2006 (34)	Endobronchial, NSCLC, Stages III	All: 95 n=65 n=15 n=15	EBRT (30 Gy/10#) EBRT (30 Gy/10#) + 10 Gy/1# @ 1 cm BT 15 Gy/1#	8 mos	10 mos	0%	No other	61% reduction in obstruction score	SOB: 93% Cough: 81% Hemop 97% Obstructive pneumonia: 91%
Allison <i>et al.</i> , 2004 (35)	NSCLC endobronchial recurrence	10	18/3#	NR	10.5	NR	NR	NR	NR
Magne <i>et al.</i> , 2003 (36)	Pall+curative	31	LDR (n=13) + HDR (n=18) HDR: 36/6# LDR: 21/3#	3.5 yrs	23 mos	16% severe Hemop	22.5%; 6%=PTx 31% stenosis	NR	NR
Gejerman <i>et al.</i> , 2002 (37)	Locally advanced or metastatic lung cancer	33	15/3# q1wk + EBRT (37.5 Gy/15#)	12 mos	Med 5.2 mos	NR	64% odynophagia-fluconazole	54%	72%
Celebioglu <i>et al.</i> , 2002 (38)	Inoperable lung cancer	95	22.5/3# vs. 20/2#	Mean 7.5 mos	NR	3%-Admission	3% (hemoptysis only)	NR (but significant improvement)	NR (but significant improvement)
Harms <i>et al.</i> , 2000 (39)	(I) prior Rx; (II) palliative new; max 3 cm periluminal extension NSCLC	55	(I) BT: 5-27 Gy (med=20); (II) 10-20 Gy (med=15)	12.6 mos	Med A1: 5 mos B1: 20 mos	0% (from DP only)	A: 0% B: 6% gr 1-2. no gr 3-4	A1: CR+PR 53% B1: 77%	NR
Kelly <i>et al.</i> , 2000 (38)	Recurrent/mets, MD Anderson	175	BT alone: 30 Gy/2#	NR	Mean 6 mos	5% fHemop	11%	78%	66% (32% much improved; 34% slight improved)
Hennequin <i>et al.</i> , 1998 (39)	Biopsy proven bronchial malignancies (SCLC 2%, Sq 88%, prior EBR 75%)	149	Mostly @ 1 cm (range, 0.5-1.5 cm)	NR	NR	7.4%	NR	NR	NR
Taulelle <i>et al.</i> , 1998 (40)	Stages I-IV lung cancer, 90% with symptoms of endobronchial disease (SCLC 6%), Sq 84%, WHO ≥2 53%, prior EBR 62%	189	6-10 Gy @ 1 cm q1w x 2-6	NR	NR	Massive hem 7%	NR	NR	74%

Table 3 (continued)

Table 3 (continued)

Author, year	Disease description	N	HDRE/EBR treatment	Median FU (mos)	Med OS (mos)	Toxicity hemoptysis (%)	Toxicity (%)	Tumour resp (%)	Symptom response (%)
DeLclos et al., 1996 (41)	Recurrent endobronchial	81	15 Gy x 2# (30 Gy) @ 6 mm	NR	NR	NR	n=2 grade 5 (fistula and tracheal malacia)	NR	Total=84% 32%=excellent 31%=moderate 21%=minimal median Duration=4.5 mos NR
Macha et al., 1995 (42)	Recurrent bronchial carcinoma, Sq 65%, SCLC 9%, majority had prior EBR	365	5 Gy @ 1 cm x 3 (G1) or x 4 (G2) q2w	NR	NR	NR	NR	NR	NR
Gollins et al., 1994 (43)	Inoperable, primary endobronchial or endotracheal, Sq 87%, NSCLC 6.5%, Stages II-IV (IV 81%), prior EBR 20%	406	Group 1 N=324 (80%) previously no-RT -> 1x BT (I) n=218; 1x BT (II) n=106; further EBRT/BT Group 2 (n=65); prior EBRT, now treated with BT Median= 15 Gy/1# (10-20 Gy) qd @ 1 cm Group 3: EBRT (30/8#-50/16#) + BT	NR	Med OS: 5.8 mos 2-yr: 7.2% 5-yr: 1%	fHemop 7.9%	Worsening SOB 5% removing of necrotic debris 0.2%	NR	@ 6 wks: GROUP 1: 92% stridor 88% hemoptysis 62% cough 60% SOB 50% pain 46% atelectasis GROUP 2: 75% stridor 88% hemoptysis 55% cough 52% SOB 60% pain 7% atelectasis
Chang et al., 1994 (44)	Primary lung cancer curative/palliative	76	Median 7 Gy x3# (21 Gy) @ 1 cm if curative, add EBRT 60-70 Gy if pall, add EBRT 20-59 Gy	Mean 7.8 mos	Mean 5 mos	4% fHemop (BT same week as EBRT) 1% mild hemop	4% pneumonitis-steroid 3% mod esoph overall)	CR 35% PR 52% (87% overall)	95% hemoptysis 79% cough 87% SOB 88% post-obs pneumonia

A/E, adverse events; BID, twice a day; BT, brachytherapy; chemo: chemotherapy; CI, confidence interval; CRT, chemoradiation EBRT, external beam radiation; Gy, Gray; mo(s), month(s); fHemop, fatal hemoptysis; n, number of patients; HDR, high-dose rate brachytherapy; Hemop, hemoptysis; KPS, Karnofsky performance status; LDR, low-dose rate brachytherapy; NR, not reported; NS, not significant; NSCLC, non-small cell lung cancer; q, every; OS, overall survival; PD, progression of disease; PDT, photodynamic therapy; PTX, pneumothorax; resp, response; RFA, radiofrequency ablation; Rx, treatment; SOB, shortness of breath; Sq, squamous cell carcinoma; symp, symptom; Sx, surgery; wk(s), week(s); *, statistically significant; #, fraction(s)

and fatal hemoptysis rate was lower (12% *vs.* 18%), although it did not reach statistical significance. Niemoeller *et al.* attributed the difference in the results to a higher irradiation dose per fraction. It is also possible that the larger sample size of Niemoeller's cohort and the difference in the randomization method—performance status in each group was not described and not accounted for—may explain these different findings.

More prospective randomised studies are needed to establish the optimal dose and fractionation can give the best palliation with minimal toxicity in advanced lung cancer.

ILBT-related toxicities

Acute toxicities

One of the most attractive characteristic of ILBT is its sharp dose fall-off curve. It is thus not surprising that its acute toxicities are relatively limited. Although acute bronchitis or pneumonitis has been reported in up to 46% of patients treated (10,31,43), these episodes were usually self-limited or readily treated with inhaled bronchodilators or steroids. Incidences of rapid necrosis of tumours sometimes requiring bronchoscopic removal of the debris have been reported in up to 5% of cases (26,43); patients generally improved after the procedure. Small risks of procedure-related complications such as pneumothorax, infection, empyema and abscess has been reported in up to 6% of cases (12,19,36,45).

Long-term toxicities

The most significant long-term toxicities include fibrosis causing stenosis, fistulisation and fatal hemoptysis.

Rates of bronchial fibrosis causing stenosis range from 2-56% (31,36,45). In most, patients are asymptomatic or minimally symptomatic thus not requiring any intervention. Fistulisation is a more significant complication, as it may lead to uncontrolled infections that may be fatal, albeit these are rare occurrences (41). Rates of fistula are relatively rare, ranging from 1-11% and were not fatal in most series (10,15,16,23,46).

One of most significant toxicity from ILBT consists of hemoptysis that may be fatal. It can occur as soon as a few weeks after ILBT and as late as almost 1 year post-ILBT. Rates of fatal hemoptysis are highly variable and in some series, can be up to 19-33% (7,21,24,31). Ornelas *et al.* (9) suggested that prior laser treatments increased the risk of fatal hemoptysis. Dose prescription point is important in

preventing fatal hemoptysis although this has not been tested in a clinical setting. Hemoptysis also occurs due to disease progression and invasion of blood vessels by tumour and not necessarily from ILBT. In most series, incidences of massive hemoptysis ranged between 2-10% and were almost invariable fatal.

Role of ILBT alone or in conjunction with other modalities in a radical setting

While the most common use of ILBT remains in a palliative setting, small series have reported outcomes of patients treated with EBBT either alone or as a boost to EBRT alone, as shown in *Table 4*.

Kawamura *et al.* (48) have previously reported outcomes of 13 patients with small endobronchial squamous cell carcinomas treated with EBRT and ILBT or ILBT alone. The median ILBT dose was 20 Gy in four fractions and 25 Gy in 5 fractions, respectively. The median dose was 45 Gy (range, 40-61 Gy), delivered at 2 Gy/fraction. The 2-year overall survival (OS) and 2-year LC were 92% and 86%, respectively. The 2-year LC was slightly higher for patients treated with EBRT-ILBT compared to ILBT alone (89% *vs.* 80%). One patient who experience airway stenosis causing cough (n=1/13) and another patient experience dyspnea grade 3 after treatments.

Perol *et al.* (45) reported prospective data on outcomes of 18 patients treated with ILBT alone with a dose escalation scheme from 21 to 35 Gy, prescribed at 1cm from the source axis and delivered at 7 Gy per fraction, weekly. The 2-year LC and OS rates were of 75% and 58%, respectively. Moreover, two patients developed major necrosis of their bronchial wall and two patients died after an episode of fatal hemoptysis. When comparing these results to those of patients treated with stereotactic body radiotherapy in other studies (49), patients treated with ILBT had a lower LC and OS rates. Furthermore, the occurrences of fatal toxicities were relatively high. Further studies are needed to evaluate the role of ILBT in a curative setting. Until further evidence is available, ILBT should be used on a case-by-case basis, and offered only when other better-established treatments such as surgery or stereotactic body radiotherapy have been deemed not feasible.

Fernando *et al.* (50) have reported outcomes of 224 high-risk operable patients with T1-3N0 NSCLC treated with sublobar resection with or without intraoperative brachytherapy (IOBT). The primary endpoint of this study was to assess whether IOBT improved local recurrence

Table 4 Studies describing outcomes of patients treated with brachytherapy with a curative intent

Author (study)	n	Tumour	Treatments	FU (mos)	LC (%)	Tumour resp	Sympt resp	OS (%)	Acute A/E	Long-term A/E
Anacak <i>et al.</i> , 2001 (47) (P)	30	NSCLC stage III	60 Gy + 15 Gy/3#	NR	Median locoregional-free survival: 9 mos	NR	Cough: 43% SOB: 80% Hemop: 95% Chest pain: 88%	Median 11 mos	Bronchitis (70%), esophagitis (6%)	Bronchial fibrosis (25%), esophageal fibrosis (13%), fHemop (11%)
Perol <i>et al.</i> , 1997 (45), pilot study (P)	18	NSCLC <1 cm, exclusive endobronchial involvement (no disease on CT-scan in lung/LNs) with C/A to other therapies	(I) 7 Gy x 3# (21 Gy) (II) 7 Gy x 4# (28 Gy) (III) 7 Gy x 5# (35 Gy) q1wk # @ 1 cm	Mean 28 mos	75%	pCR 83%	NR	1-yr: 78% 2-yr: 58%	n=1 fatal hemoptysis n=1 slight PTx (undrained) n=1 bronchial infection	• Asymptomatic partial fibrous stenosis 10/18 (56%) • n=2 major necrosis of bronchial wall • n=2 fHemop
Kawamura <i>et al.</i> , 2012 (48) (R)	13	SCC endobronchial ca'a <2 cm Roentgenographically occult early endobronchial cancer	n=10: EBRT (median = 45 Gy/22#, range, 40-61 Gy/18-30#) + BT [5 Gy x4=20 Gy (median)] n=6: BT alone (median 5 Gy x5=25 Gy/wk	Median 32.5 mos	86% BT alone =80% EBRT + BT =89%			2-year OS 92%	(1/13) SOB grade 3 causing cough grade 2	

A/E, adverse event; BT, brachytherapy; C/A, contraindications; EBRT, external beam radiotherapy; fHemop, fatal hemoptysis; FU, follow-up; LC, local control; n: number of patients; mos, months; NR, not reported; NSCLC, non-small cell lung cancer; OS, overall survival; (P), prospective study; PTx, pneumothorax; (R), retrospective study; resp, response; SCC, squamous cell carcinoma; SOB, shortness of breath; sympt, symptom; wk, week; #, fraction.

rates or not. The dosimetry goal of IOBT was to deliver 100 Gy at 5-7 mm along the central axis of the resection margin. IOBT did not reduce local recurrence rates or time to recurrence (HR 1.01; 95% CI 0.51-1.98, P=0.98) nor did it improve 3-year OS rates (71% vs. 71%, P=0.97)

In summary, the role of ILBT in curative treatments remains investigational. Its use alone to treat radically endobronchial tumours is not well established and should not be routinely practiced other than in a clinical trial or if the patient is unsuited for surgery/radical chemoradiation due to any reason. ILBT may be considered either as a boost for endoluminal tumours or post-operatively, if they are not candidates for EBRT. These treatments should be delivered within a clinical trial to document outcomes of these patients.

Conclusions

In conclusion, the current evidence mainly supports the use of ILBT in a palliative setting mostly in combination with other treatments modality, such as EBRT (most commonly) and Nd-YAG laser. When delivered with EBRT, it improves rates of lung re-oxygenation and LC without significantly increasing toxicities. Its role in a radical setting remains investigational. Further studies are required to determine the optimal dose fractionation scheme.

Acknowledgements

None.

Footnote

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

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Cite this article as: Nguyen NT, Sur RK. Brachytherapy in lung cancer: a review. *Transl Cancer Res* 2015;4(4):381-396. doi: 10.3978/j.issn.2218-676X.2015.08.08

Advances in radiotherapy techniques and delivery for non-small cell lung cancer: benefits of intensity-modulated radiation therapy, proton therapy, and stereotactic body radiation therapy

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Contributions: (I) Conception and design: S Feigenberg, SN Badiyan, P Mohindra, TP Diwanji; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All Authors; (V) Data analysis and interpretation: All Authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: The 21st century has seen several paradigm shifts in the treatment of non-small cell lung cancer (NSCLC) in early-stage inoperable disease, definitive locally advanced disease, and the postoperative setting. A key driver in improvement of local disease control has been the significant evolution of radiation therapy techniques in the last three decades, allowing for delivery of definitive radiation doses while limiting exposure of normal tissues. For patients with locally-advanced NSCLC, the advent of volumetric imaging techniques has allowed a shift from 2-dimensional approaches to 3-dimensional conformal radiation therapy (3DCRT). The next generation of 3DCRT, intensity-modulated radiation therapy and volumetric-modulated arc therapy (VMAT), have enabled even more conformal radiation delivery. Clinical evidence has shown that this can improve the quality of life for patients undergoing definitive management of lung cancer. In the early-stage setting, conventional fractionation led to poor outcomes. Evaluation of altered dose fractionation with the previously noted technology advances led to advent of stereotactic body radiation therapy (SBRT). This technique has dramatically improved local control and expanded treatment options for inoperable, early-stage patients. The recent development of proton therapy has opened new avenues for improving conformity and the therapeutic ratio. Evolution of newer proton therapy techniques, such as pencil-beam scanning (PBS), could improve tolerability and possibly allow reexamination of dose escalation. These new progresses, along with significant advances in systemic therapies, have improved survival for lung cancer patients across the spectrum of non-metastatic disease. They have also brought to light new challenges and avenues for further research and improvement.

Keywords: Non-small cell lung cancer (NSCLC); stereotactic body radiation therapy (SBRT); proton therapy; intensity-modulated radiation therapy (IMRT)

Submitted Nov 05, 2016. Accepted for publication Mar 17, 2017.

doi: 10.21037/tlcr.2017.04.04

View this article at: <http://dx.doi.org/10.21037/tlcr.2017.04.04>

Introduction

The 21st century has seen several paradigm shifts in the treatment of non-small cell lung cancer (NSCLC) in early-stage inoperable disease, definitive locally advanced disease, and the postoperative setting. Patients

are increasingly being treated with curative intent rather than palliation. Survival has improved in advanced stages with more aggressive approaches involving combinations of chemotherapy and thoracic radiotherapy (RT) (1). Several chemotherapy agents developed during the 1990s

demonstrated enhanced activity. In addition, the birth of immunotherapy and targeted therapy has revolutionized the treatment of advanced lung cancer. Improved survival rates for inoperable patients with stage III NSCLC have been realized by using “conventional” radiation techniques (2-5) involving the standard dose of 60 Gy delivered over 6 weeks. This dose of radiation was found to be most efficacious in dose-escalation trials in the 1970s and did not change significantly for 20 years. Initial radiation therapy approaches utilized 2-dimensional (2D) imaging for the design of treatment fields. The inherent problems in visualization of tumor and nodal disease on a 2D radiograph necessitated larger radiation fields to cover uncertainty and minimize marginal failures. The tradeoff with these larger fields was an increase in toxicity, which limited use of higher radiation doses.

Local tumor control remained suboptimal in patients treated with conventional RT (even with the addition of chemotherapy) which resulted in renewed interest in strategies to improve local treatment (5). A key driver in the improvement of local control has been the significant evolution in radiation techniques in the last three decades, allowing delivery of more effective radiation doses while limiting doses to normal tissues. With the advent of image-guided radiation therapy (IGRT), techniques have moved from 2D approaches to 3-dimensional conformal RT (3DCRT). The next generation of 3DCRT, intensity-modulated RT (IMRT) and volumetric-modulated arc therapy (VMAT), have enabled even more conformal radiation delivery. Evaluation of altered dose fractionation with these technology advances led to the development of stereotactic body RT (SBRT) for early-stage lung cancer. The recent advent of pencil-beam scanning (PBS) proton therapy has opened new avenues for improving conformity and the therapeutic ratio. SBRT and PBS techniques have placed significant emphasis on motion management, which continues to be among the biggest technical challenges in the use of advanced radiation modalities in lung cancer. Novel monitoring and mitigation strategies have provided the possibility of reducing morbidity/mortality using the standard dose, as well as the possibility of safely escalating the dose to improve oncologic outcomes.

This article reviews the technical advances in RT, their clinical impact, and the associated possibilities for future research in NSCLC. We will focus on progression from 3DCRT to IMRT/VMAT in definitive management of advanced disease, the utility of SBRT in early-stage

inoperable disease, and the advent of proton therapy and its role in early- and late-stage disease.

Technical comparison: 3DCRT and IMRT

3DCRT and challenges

Conventional RT for lung cancer, developed in the 1970s before adoption of computed tomography (CT) for treatment planning, was supplanted by 3DCRT, which uses 3D patient-specific geometry in treatment planning. Despite this progression from conventional RT, limited beam arrangements and uniform dose in each beam in 3DCRT can lead to high doses to organs at risk (OARs) (i.e., normal lungs, heart, spinal cord, and esophagus) because of the simple and relatively large fields (6,7). Several pioneers of the early 3DCRT era published predictors of complications (8-14). Graham *et al.* from Washington University in 1999 demonstrated a correlation between the volume of lung receiving 20 Gy and rates of pneumonitis that remains in use today (8). This analysis demonstrated an 8% rate of grade 3 pneumonitis in patients whose lung volume receiving greater than 20 Gy (V20) was between 22–31%, as compared to 23% for patients whose V20 was >40%. Furthermore, no patients with V20 <32% had grade 5 toxicity. Wang *et al.* performed a retrospective investigation in 223 NSCLC patients treated with concurrent chemotherapy and 3DCRT and found the incidence of grade 3 or higher pneumonitis for patients with V20 >28% was 37% compared to 4% in patients with V20 ≤28% (14). This high risk of complications translated to poor outcomes from increased morbidity and mortality in patients whose disease was controlled. A significant risk of local failures, suggesting a possible utility to dose escalation, was also noted; however, the already high rates of toxicity meant that newer techniques would be required that could change the therapeutic ratio. For these reasons, considerable interest focused on developing and applying treatment planning and delivery techniques that could improve dose conformality (e.g., IMRT).

IMRT is an increasingly common method of lung cancer treatment for both early-stage and locally advanced NSCLC. IMRT treatment plans use advanced technology to modify the intensity of each photon beam via dose-rate alterations and field modulation with multileaf collimators (MLCs). The two main types of IMRT delivery are static and dynamic (or VMAT). Although VMAT has treatment time advantages over static IMRT delivery, no evidence

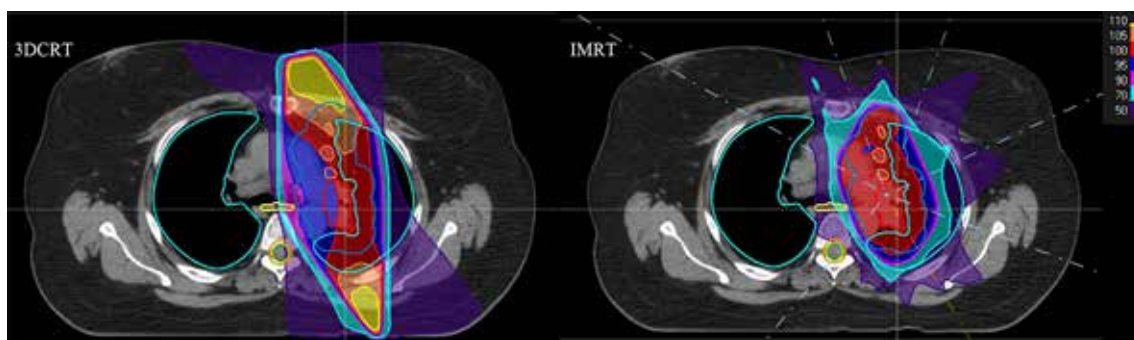


Figure 1 Improved conformity of the high-dose region to the target volume and improved sparing of organs at risk with intensity-modulated radiation therapy compared to 3-dimensional conformal radiation therapy. Gross tumor volume including nodal disease is depicted by the red/orange contour. Spinal cord is depicted by the green contour. Esophagus is depicted by the yellow contour. The relative isodose is depicted in colorwash as per the color scale in the picture.

indicates definitive superiority of one technique over the other (15-18). Regardless of IMRT technique, treatment plans are usually inversely optimized by a treatment planning system and generate conformal dose distributions with sharper dose falloff around treatment structures, thereby theoretically reducing collateral dose to normal tissue and resulting morbidity associated with radiation dose to OARs (*Figure 1*: esophagus and spinal cord) (13,19-21).

To test the hypothesis of reduced OAR dose with IMRT, several studies have compared the dosimetry of 3DCRT and IMRT in treating NSCLC (22-25). Grills *et al.* showed that IMRT can reduce the lung V20 by 15% and esophagus V50 by 40% in node-positive patients (23). Christian *et al.* evaluated five IMRT plans using three, five, seven, and nine equally spaced coplanar beams and one plan with non-coplanar beams and compared them to six-field, inversely planned, 3DCRT plans for 10 patients (26). Their results demonstrated that the ratio of the percentage of the planning target volume (PTV) covered by the 90% isodose line to the percentage of lung volume receiving 20 Gy (PTV 90/V20) was significantly better in all IMRT plans, except those with three fields, when compared with equivalent 3DCRT plans. Regarding the benefit of an increase in the number of beams in IMRT plans for NSCLC, they showed an increase in PTV90/V20 ratio with the increase in the number of equally spaced coplanar beams. They found that nine beams provided the optimal solution in six of the 10 cases; however, they cautioned that increasing setup times, as well as the risk of increased systematic and random errors, may mitigate the marginal increase in benefit (26). More importantly, they also noted that IMRT plans with <5 beams conferred no notable benefit “compared with

beam-angle optimized 3DCRT plans” (26).

Numerous techniques have been developed recently that can leverage the advantages of IMRT with the dynamic motion of MLCs and simultaneous motion of the X-ray source. Intensity-modulated arc therapy (IMAT) is an alternative to tomotherapy proposed by Yu that delivers the radiation dose through single or multiple arcs along with MLC-based modulation to conform the beam to the target and to block critical structures (27). VMAT, as developed by Otto, is a single-arc form of IMAT that also uses a variable dose rate to modulate radiation dose delivery (28).

Motion management and mitigation

These advanced techniques, including VMAT and IMRT, allow delivery of more complex plans while simultaneously decreasing treatment times. In the treatment of NSCLC, however, they heighten concerns about the effects of motion interplay on IMRT delivery. Unlike 3DCRT plans that encompass the entire target through each beam, IMRT plans may block certain regions of the target from certain beams or arc angles (29). These concerns have led to the development of a variety of motion management and mitigation techniques. Breath-hold and abdominal compression are two common methods to reduce tumor motion and, thereby, the average dose to normal lung tissue (30,31). Other management strategies include acquiring 4-dimensional CT (4DCT) to identify tumor motion during breathing cycles and to allow a better estimation of dose delivery to tumors and normal structures (32-37). All of these methods have shown significantly reduced lung V20 (31,38). Finally, significant research exists on beam gating and tumor tracking (39-42). However, inherent

irregularities in patient breathing patterns and the intrinsic delay in dose delivery (i.e., MLC and gantry motion) can lead to increased treatment times and necessitate development of class solutions that are predictive in nature (43-45). Techniques to minimize breathing irregularity including biofeedback and active breathing control may offer additional benefits in improving inter- and intra-fraction reproducibility but additional work to improve reproducibility is needed (46-48). Ongoing research may elucidate techniques that can effectively reduce normal tissue dose without compromising treatment efficiency.

Impact of heterogeneity correction

The increasing complexity of treatment plans results in increasing dependency on accurate dose modeling. One significant advance on this front has been determining the impact of heterogeneous tissue density on dose delivery. Differences in dose calculations with and without heterogeneity corrections for IMRT and SBRT treatments in NSCLC patients have been investigated in several studies that have uniformly demonstrated the necessity for advanced algorithms with heterogeneity corrections to achieve accurate dose calculations (49-54). Vanderstraeten *et al.* compared full Monte Carlo calculations with two different convolution/superposition algorithms and one pencil-beam algorithm for 10 lung cancer patients receiving IMRT (55). They found a better agreement between convolution/superposition and Monte Carlo methods for dose calculation within the target structures. They concluded that none of the dose calculation algorithms could provide results within 5% of the Monte Carlo calculations, and therefore it is imperative to be aware of the impact of the dose calculation algorithm on plan evaluation. Davidson *et al.* determined the accuracy of heterogeneity on dose calculations from two IMRT treatment planning systems against thermoluminescent detectors and radiochromic film measurements positioned in a lung phantom (56). They found that the collapsed cone convolution/superposition dose calculation algorithm provided clinically acceptable results within $\pm 5\%$ of the measurements. They also demonstrated that the pencil-beam algorithm as tested may overestimate the dose to the target. Although Monte Carlo simulations continue to serve as the gold standard for dose calculations, heterogeneity corrections have dramatically improved the accuracy of more efficient but less precise algorithms needed to successfully implement inverse planning IMRT.

Clinical evidence: 3DCRT and IMRT

Although the initial rationales for IMRT and VMAT were largely their dosimetric advantages, numerous retrospective studies have attempted to isolate the clinical benefits of IMRT over conventional external-beam radiation. Some early reports on the benefits of intensity modulation in lung cancer treatment came from the MD Anderson Cancer Center (MDACC) (13,21). Yom *et al.* reviewed rates of toxicity, particularly radiation pneumonitis, in 68 patients with advanced NSCLC treated with concurrent chemotherapy and IMRT from 2002 to 2005 (21). They found that patients treated with IMRT had dramatic and statistically significant decreases in the rate of grade 3 radiation pneumonitis at 1 year compared to 3DCRT patients (8% and 32%, respectively). Liao *et al.* then evaluated an expanded cohort of 496 patients treated between 1999 and 2006, with 318 receiving 3DCRT and 91 receiving 4DCT/IMRT. Their report demonstrated a statistically significant improvement in overall survival (OS), with a hazard ratio of 0.64 (95% CI, 0.41–0.98) when treated with IMRT (13).

The advent of 3DCRT and consequent improvements in toxicity profiles also initiated a series of phase I and II dose-escalation trials that occurred in parallel with development of IMRT. Several authors showed that with the same dose constraints, up to 35% greater RT doses could be given to the target with IMRT than 3DCRT, with the aim of improving local control (23,25,57). Armed with this favorable dosimetric data on toxicity and significant improvements already demonstrated with 3DCRT, several institutions initiated dose-escalation trials in the 1990s and 2000s.

The Radiation Therapy Oncology Group (RTOG) conducted a phase I/II study of dose escalation without concurrent chemotherapy (58) in 177 patients treated using 3DCRT to doses ranging from 70.9 to 90.3 Gy. The results demonstrated that it was safe to escalate radiation dose to 83.8 Gy with a lung V20 of <25% and to 77.4 Gy if the planned lung V20 was between 25% and 36%. Equally important, 90.3 Gy, the highest dose tested, was determined to be too toxic on the basis of two grade 5 toxicities in that population. The safety of dose escalation in the absence of concurrent chemotherapy was also verified by University of Michigan researchers, who escalated the radiation dose from 63 to 103 Gy in 2.1-Gy fractions (59). Most patients (81%) did not receive neoadjuvant chemotherapy. The authors demonstrated improved local control and OS with

higher doses of radiation when patients were divided into three treatment groups (63–69, 74–84, and 92–103 Gy).

The cited studies demonstrated the potential safety and efficacy of dose escalation in lung cancer without concurrent chemotherapy; in the same period, emerging data also indicated a benefit for concurrent chemotherapy. Dose escalation in the setting of concurrent chemotherapy was believed by some to be challenging because of increased risks of cardiopulmonary and esophageal toxicity and the possibility that synergistic effects on tumors could be overshadowed by increased rates of adverse effects. Three phase I/II trials with concurrent chemotherapy were undertaken by RTOG, the University of North Carolina (UNC), and the North Central Cancer Treatment Group (NCCTG) (60–62). RTOG 0117 was designed as a combined phase I/II trial and enrolled 8 patients in cohort 1 of the phase I portion of the trial (60). These patients were treated to a dose of 75.25 Gy in 35 fractions. Two major pulmonary toxicities (grade 3 and grade 5) occurred, leading to a reduction in dose to 74 Gy in 37 fractions. An additional 9 patients were enrolled in the phase I cohort 2, with only one experiencing dose-limiting toxicity (grade 3 esophagitis). The phase II component enrolled a total of 55 patients in the 74-Gy arm, of whom 53 were evaluable (60). This portion of the study showed a median OS of 21.6 months with a more acceptable 10% \geq grade 3 lung toxicity. Similarly, the NCCTG designed a phase I trial to escalate the RT dose from 70 to 78 Gy and found unacceptably high toxicities (50%; 2 of 4 patients) at a dose of 78 Gy (62). Like the RTOG, they concluded that 74 Gy was a safe and tolerable dose. The UNC phase I trial also demonstrated that 74 Gy was a safe dose with concurrent chemotherapy (61).

On the basis of these trials, RTOG launched a phase III trial (RTOG 0617) to determine the benefit of dose-escalated RT utilizing the 74-Gy dose and assessing the benefit of cetuximab (63). The trial was stopped prematurely when results crossed the prespecified boundary for futility. Median OS was 28.7 months in the standard dose (60 Gy) arm and 20.3 months in the dose-escalation arm. Toxicity, particularly severe esophagitis, was more prevalent in the 74 Gy arm (21%) than the 60 Gy arm (7%). Pulmonary toxicity did not differ statistically but marginally favored the standard-dose arm. Despite early termination, this study raised critical questions about dose and toxicity. Of particular importance were questions on rates of completion of prescribed chemoradiation and concerns about volume of disease, adequacy of margins, and heart dose, with

associated cardiac morbidity. A recent secondary analysis of this trial further demonstrated that IMRT was associated with lower cardiac doses and pulmonary toxicities (64). The cardiac dose, particularly V40, was further linked with OS on adjusted analysis (64). Notably, this was despite larger PTV, higher PTV/volume of lung ratio, and more stage IIIB disease in patients receiving IMRT (64). Lastly, there was no difference in OS between IMRT and 3DCRT.

Additional secondary analysis on differences in quality of life (QOL) in the standard- and high-dose arms revealed a correlation between baseline QOL and outcomes (65). The authors also demonstrated that, despite the absence of dramatic differences in physician-graded toxicity profiles, patient-reported QOL was meaningfully and statistically significantly lower in the high-dose arm at 3 months. Participants in the RTOG 0617 trial were stratified by receipt of IMRT or 3DCRT. When the QOL of these two groups was compared using the Functional Assessment of Cancer Therapy-Lung Cancer Subscale, fewer patients in the IMRT arm experienced a decline (21% and 46%, respectively; $P=0.003$). Overall IMRT utilization was similar in the 60- and 74-Gy arms (44.1% and 46.0%, respectively). The difference in QOL, however, occurred despite certain imbalances favoring the 3DCRT group over the IMRT group such as lower PTV volumes [409 and 509 cc, respectively ($P<0.001$)] and fewer stage IIIB patients [31% and 43%, respectively ($P=0.04$)]. Finally, the lower proportion of decline in QOL was persistent for patients receiving IMRT at 12 months, and treatment modality (IMRT or 3DCRT) remained significant in multivariate logistic regression models.

Future directions

Strong emphasis has been placed on determining the cause of decreased survival in the high-dose arm of the RTOG 0617 trial. This is likely to drive further work in not only identifying dosimetric parameters but also innovations in reliably characterizing and quantifying cardiopulmonary toxicity from RT. One increasingly used method is cardiac magnetic resonance imaging, which offers the possibility of evaluating characteristics such as late fibrosis and tissue perfusion. These metrics may help increase sensitivity for detection of radiation-associated cardiac complications beyond frank ischemic changes. Motion management and mitigation will also play a significant role in decreasing dose to surrounding uninvolved lung, and predictive strategies will be integral to minimizing target volumes. Functional

lung imaging may help leverage the inherent heterogeneity of lung function to minimize consequences from normal tissue irradiation. Parallel research into development of radiation toxicity mitigators is underway and may further improve the therapeutic ratio and potentially allow re-evaluation of dose escalation in the future. The next generation of treatment planning is already being investigated and could help further reduce intermediate dose regions despite the potential downside of a larger low-dose bath. One such modality, 4π , involves the use of a highly non-coplanar planning system that utilizes the entire 4π solid angle space in an attempt to improve high-dose conformality at the expense of increased treatment time (66). Much work remains to be done, but dosimetric studies are increasingly highlighting the advantages of 4π treatment planning techniques (67).

SBRT

Introduction

SBRT or stereotactic ablative RT (SABR) is a technique for delivering a high biologically effective dose (BED; usually $BED > 100 \text{ Gy}_{10}$ in contrast to a BED of 72 Gy_{10} with 60-Gy conventional fractionation) to well-localized early-stage NSCLC lesions. SBRT has developed into an excellent option for patients with early-stage NSCLC, especially in cases deemed medically or surgically inoperable. Stereotactic treatment offers the advantage of higher doses per fraction, decreased overall treatment time, and steep dose gradients. However, uncertainty remains over SBRT's superiority to other modes of treatment, such as surgical resection, which remains the standard of care for stage I disease.

SBRT technique

SBRT can be delivered using a 3DCRT, IMRT, or VMAT approach. Typically for the 3DCRT technique, 8–15 static beams are used to generate conformal dose distributions and steep dose gradients. Six megavolt energies are desired over higher energies because of the sharper penumbra resulting from less lateral electron transport (i.e., secondary electrons are lower energy and travel shorter distances). The individual beams are non-opposed, separated by 20° – 30° , and can be coplanar or non-coplanar. Non-coplanar beams have the advantage of increasing the conformality of the

high-dose region but should be used with caution because of inherent shortcomings, including difficulties with portal imaging and associated increase in setup uncertainty, potential for collision and inadequate gantry clearance, possibly longer beam paths, and theoretically longer treatment times.

Beam weighting is adjusted to achieve optimal coverage while minimizing dose to critical structures. The prescription point is also an important consideration for SBRT. In the United States, dose is usually prescribed to between 60% and 90% isodose lines, although the initial Japanese (JCOG 0403) study prescribed to the isocenter (68). Additionally, coverage of the PTV is usually set so that 95% of the PTV is covered by the prescription dose and 99% of the PTV receives at least 90% of the dose. The hot spot is ideally placed in the gross tumor volume (GTV) or should fall within the PTV. To generate rapid falloff, the 50% isodose line can be analyzed to make it conformal around the lesion with few spikes (*Figure 2*). In order to generate the steep gradient, there is very little margin around the target to account for penumbra. Alternative techniques involve prescribing to lower isodose lines, which can also improve dose falloff (69). The dose prescription for SBRT fractionation varies depending on whether the tumor is peripherally located in the chest (25 – $34 \text{ Gy} \times 1$ fraction, $18 \text{ Gy} \times 3$ fractions, 12 – $12.5 \text{ Gy} \times 4$ fractions, or 10 – $12 \text{ Gy} \times 5$ fractions) or centrally located (10 – $12 \text{ Gy} \times 5$ fractions). Because of the high doses involved, tumor size is typically limited to $< 5 \text{ cm}$ in diameter, which prevents overinclusion of treated healthy tissue (70–72).

IMRT/VMAT-based SBRT techniques may have advantages compared with 3DCRT in paraspinal patients in whom motion is limited and where dose constraints to esophagus or spinal cord cannot be achieved. IMRT has the advantage of better coverage of irregular-shaped targets. This approach has also been utilized for peripheral tumors to help reduce dose to the ribs/chest wall. VMAT has the advantage of delivering a beam of radiation over a 358° arc with simultaneous movement of the MLC with varying gantry speed and dose rate. This leads to a reduction in treatment time with increased OAR sparing. And while analyses comparing the impact of technique on normal lung dosimetry are limited, initial results are mixed and warrant careful consideration of the low-dose bath (17,73). Using IMRT/VMAT requires attention to positional misses and uncertainty in dose delivery because of the interplay between MLC movement and respiratory tumor

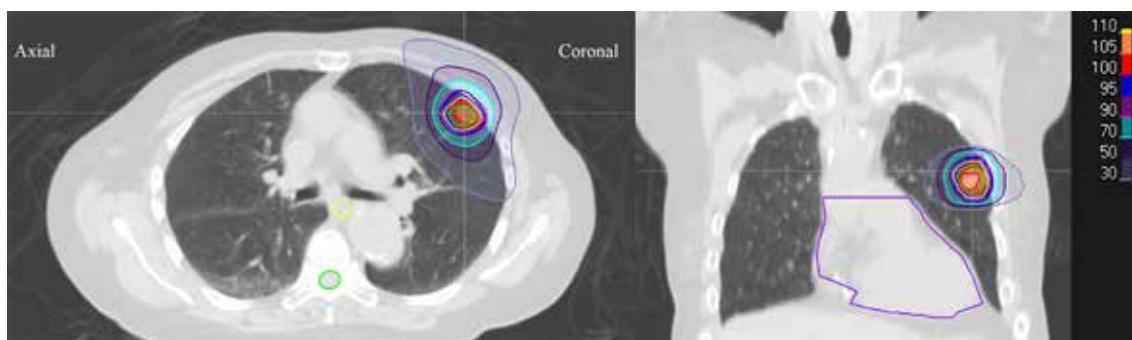


Figure 2 Representative axial and coronal slices demonstrating the dose distribution in a stereotactic body radiation therapy plan. Gross tumor volume including nodal disease is depicted by the red contour. Spinal cord is depicted by the green contour. Esophagus is depicted by the yellow contour. Heart is depicted by the purple contour. The relative isodose is depicted in colorwash as per the color scale in the picture.

motion, as well as dosimetric inaccuracy resulting from tissue heterogeneity and small field sizes. Furthermore, compared with conventionally fractionated therapy, fewer fractions limit the degree of dose-averaging for SBRT regimens. IMRT and VMAT also require significantly more technical resources for planning, quality assurance, and delivery of treatment (74). Lastly, clinical data comparing techniques are limited, and while retrospective data suggest adequate rates of tumor control and toxicity (75), careful consideration of motion mitigation and caution when using modulated beams in tumors with significant (>1 cm) motion are recommended.

The challenges of SBRT treatment planning (i.e., geometric miss, dose heterogeneity, and normal lung dose) are accentuated by the high dose per fraction and low number of fractions. Reliable geometry is of paramount importance in safe and accurate delivery of SBRT, and the regular use of Winston-Lutz tests to check the isocentricity of delivery (<1 mm) and online image guidance to accurately verify tumor and OAR location before and potentially during treatment play significant roles in the reliability of the system (70,76). SBRT dose calculations must also be very precise and, therefore, should include a heterogeneity correction, because lung density can vary up to 0.1× or 0.1 times that of surrounding tissue. This leads to an increased range of photons and secondary electrons that can blur beam edges. Tissue heterogeneity correction depends on beam energy, field size, path length, and lung density and can be calculated accurately using Monte Carlo and superposition/convolution algorithms. The dose calculation grid is frequently set to ≤ 2 mm for acceptable accuracy (within 1%) (77).

Clinical evidence for SBRT

A number of retrospective reports suggest that conventional RT for early-stage NSCLC results in poor rates of local control and OS. For example, retrospective data from Duke University looked at 156 patients with stage I medically inoperable NSCLC who received a median dose of 64 Gy (range, 50–80 Gy) in 1.2-Gy twice-daily or 3-Gy daily fractions (78). At these doses, deaths were attributed to a high rate of local failure (42%), and the researchers observed that patients with improved local control, which correlated to radiation dose received, also had improved 5-year cause-specific survival (CSS) rates. Population data further validated this; a Surveillance, Epidemiology, and End Results study looked at 4,357 patients with stage I and II NSCLC who did not undergo surgical resection but were treated with conventional RT (79). The researchers concluded that radiation offers a 5–7-month survival benefit but no cure; patients who did and did not receive RT had similar outcomes (5-year OS, 15%). Various literature reviews report 5-year OS to be 30–40% in early-stage NSCLC treated with conventional RT, with doses ≥ 65 Gy necessary for long-term control (80–82). These data compared adversely with historical surgical series (83–85). Moreover, despite higher doses of conventional radiation, local failure rates remained high (30–70%) (80) and clinicians started exploring the practicality of radiosurgery in treatment of early-stage NSCLC. The use of SBRT for lung cancer was first published in 1991 from clinical work started in Sweden for 42 tumors in 31 cancer patients (86). Various sites, including lung, were treated using a stereotactic body frame for fixation, and prescribed

doses, ranging from 7.7 to 30 Gy/fraction (mean, 14.2 Gy), were given for 1–4 fractions. This early work demonstrated an excellent local control rate (80%) and, more important, revealed minimal complications, suggesting the safety of such an approach. During this time, early studies were also underway in Japan, and the combination of Swedish and Japanese experience spearheaded exploration of SBRT for early-stage NSCLC (87,88).

A phase I dose escalation study from the University of Indiana was conducted on operable but medically ineligible stage IA and IB patients (tumor size <7 cm) (89). For T1 tumors, the maximum tolerated dose (MTD) was not reached (maximum dose =60 Gy), but for tumors >5 cm, the MTD was 72 Gy in 3 fractions. At the time of publication, only one local failure occurred in doses \geq 16 Gy. This work led to RTOG 0236, a phase II trial recruiting resectable but medically inoperable patients whose primary tumor was <5 cm in size and \geq 2 cm from the bronchial tree (because of high rates of grade 5 toxicities seen with centrally located tumors) (69). The radiation dose was 60 Gy in 20-Gy fractions without heterogeneity corrections (18 Gy \times 3 with corrections), and 3-year local control was 90.6%, with survival at 55.8% (90).

In this setting of numerous trials with no clear consensus on optimal dosing, retrospective data published from Japan looked at 245 stage I patients treated with 18–75 Gy targeted at the isocenter, given in 1–22 fractions (87). The group observed a local failure rate of only 8.1% for a $BED_{10} \geq 100$ Gy *vs.* 26.4% when the BED_{10} was <100 Gy. This trend was also seen in survival outcomes, where 3-year OS was 88.4% *vs.* 69.4% with $BED_{10} \geq$ or <100 Gy, respectively.

In this setting of dose escalation, numerous subsequent retrospective analyses began to demonstrate improving local control rates and survival. Grills *et al.* reviewed 124 early-stage NSCLC patients who were not eligible for a lobectomy and underwent either SBRT (n=55) or a wedge resection (n=69) (91). The authors noted better local control with SBRT (recurrence of 4% *vs.* 20%) and similar CSS in both cohorts (93% *vs.* 94%) (91). This equivalence was further supported by data from Onishi *et al.*, who retrospectively evaluated operable stage IA and IB patients treated with a mean BED_{10} of 116 Gy (range, 100–141 Gy) and reported excellent 5-year local control rates of 92%, with OS ranging from 62% to 72%, similar to surgical outcomes (92). A separate group also performed a propensity-matched analysis that compared 64 SABR patients with 64 patients who underwent a video-assisted thoracoscopic surgery lobectomy and determined that post-

SABR locoregional control rates were superior at 1 and 3 years (96.8% and 93.3% *vs.* 86.9% and 82.6%, respectively) with similar OS (93).

Because of this equivalence in survival and improved local control compared with historical surgical data, the STARS trial out of MDACC and the ROSEL trial from The Netherlands attempted to compare SBRT to surgical lobectomy in a randomized trial. Additionally an American College of Surgeons Oncology Group and RTOG combined trial (ACOSOG Z4099/RTOG1021) was also initiated to compare clinical results of SBRT to sublobar resection. Despite early termination, an exploratory QOL analysis of the 22 enrolled patients on the ROSEL trial suggested a possible advantage to SBRT, particularly in health-related QOL (94). All analyses of these trials, however, are extremely limited due to being underpowered, as all the trials closed early due to poor accrual.

To mitigate this statistical limitation, a pooled analysis of the STARS and ROSEL trials was performed with a combined total of 58 T1–T2 (<4 cm) operable patients (95). Patients were randomized in a 1:1 fashion to surgery or SBRT (54 Gy/3 fractions for peripheral lesions given over 5–8 days *vs.* 50 Gy/4 fractions or 60 Gy/5 fractions for central lesions). Surprisingly, OS for the SBRT cohort was superior to the surgical cohort, with 3-year OS of 95% in the SBRT cohort *vs.* 79% with surgery ($P < 0.05$). Toxicity rates were also lower in the SBRT arm than the surgery arm (10% and 44%, respectively, grade 3 or greater toxicities). The surgical arm also had one grade 5 toxicity. These randomized trials, although underpowered, suggest that SBRT may be better tolerated than surgery, with the possibility of improved survival.

Future work

Technological improvements will continue to drive significant innovation in the field of SBRT. To address the above technical challenges in 3DCRT/IMRT/VMAT planning and delivery for SBRT, such as reliable setup, motion management, and accurate target and normal structure delineation, new tools will be needed to improve the therapeutic ratio. Reliable and consistent patient immobilization systems, tumor motion management strategies (such as abdominal compression, breath-hold, respiratory gating, coaching with audiovisual feedback, and intra-fraction tumor-tracking real-time imaging techniques with dynamic beam and/or couch compensation), and improved imaging modalities (such as ^{18}F -FDG PET for

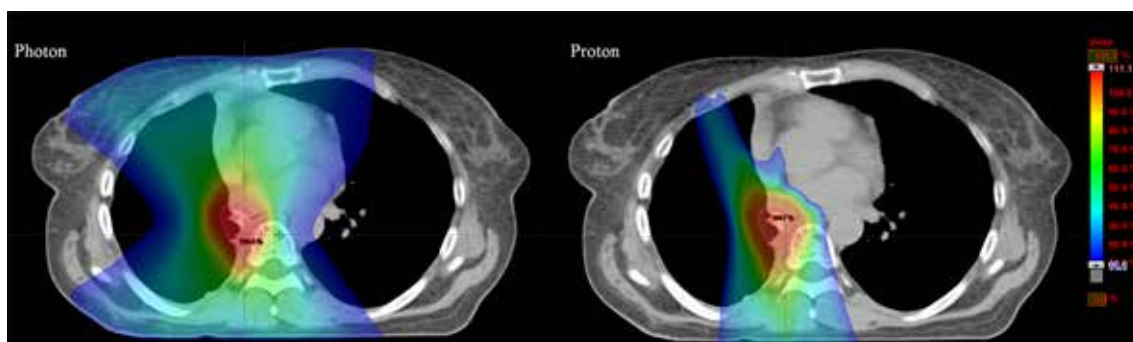


Figure 3 Proton therapy has improved the low-dose bath to the heart and lungs with relatively unchanged high-dose conformity compared with photon therapy. The relative isodose is depicted in colorwash as per the color scale in the picture.

better identification of GTV) all appear to be potential strategies to improve outcomes and decrease toxicity from SBRT. Further clinical research is needed to directly answer the question about equivalence with surgical management, and, to that end, multiple randomized trials, including STABLE-MATES, SABRTooth, VALOR (Veterans Affairs Lung Cancer Surgery Or Stereotactic Radiotherapy), and POSTILV (A Randomized Phase II Trial In Patients With Operable Stage I Non-Small Cell Lung Cancer: Radical Resection Versus Ablative Stereotactic Radiotherapy-RTOG3502), are planned or underway (96). Additionally, emerging data looking at expanding the cohort of patients eligible for SBRT [e.g., patients with central tumors (97) or tumors >5 cm (98)] are promising; and further clinical data are imminent.

Proton therapy

Introduction

Proton therapy offers a unique pattern of energy deposition, with the majority of dose delivered at the end of range, with virtually no exit dose. This property makes the modality particularly attractive for clinical use in the thorax, where numerous radiosensitive critical structures reside in close proximity to the target (i.e., uninvolved lung, heart, esophagus, spinal cord, major vessels, and chest wall) (Figure 3). Dose distributions associated with proton therapy allow the possibility of dose escalation while maintaining current levels of normal tissue exposure. As noted, recent clinical trials suggest that RT can achieve local disease control rates similar to surgical approaches with potentially less toxicity in early-stage NSCLC (90,95). Such results have correlated with significant dose escalation,

in the range of BED >100 Gy₁₀, over doses traditionally achieved with non-stereotactic techniques or in locally advanced disease (88). Results from RTOG 0617, however, have given clinicians pause in attempting to achieve higher doses with traditional 3DCRT or IMRT, considering the worsened outcomes with 74 vs. 60 Gy (63). These outcomes were attributed to, and correlated on multivariate analysis, with increased exposure of normal tissues, such as the heart and esophagus, to significant doses of radiation. These may be areas where, in well-selected patients, proton therapy could offer substantial dosimetric advantages.

Proton therapy technique

Modalities

Proton therapy can now be delivered through several methodologies. The most widely used, passive scattering (PS-PT), employs a single beam that is spread out in the depth dimension by a range-modulator wheel (spread-out Bragg peak) prior to widening in the other dimensions by a scatterer. The lateral edge of the beam is then shaped by an aperture and the distal edge by a compensator. Of note, it is not possible to conform the proximal edge of a PS-PT beam.

On the other hand, the rapidly expanding technique of PBS proton therapy, also known as “spot scanning”, employs scanning magnets to deliver discrete spots of proton beams across a 2D rectilinear grid in the vertical and lateral directions. The range is set for each layer by the energy selection system. This approach allows for both improved proximal dose conformity and intensity-modulated proton therapy (IMPT) within the target. By utilizing multifield optimization and a few (usually 2–4) highly heterogeneous fields that sum to the desired improved dose distribution,

IMPT has shown dosimetric improvements over IMRT and PS-PT in multiple *in silico* studies (99,100). However, these advantages do not come without some increase in uncertainties and diminution in robustness of plan delivery. These uncertainties are highlighted in lung cancers (101-104). In particular, several studies have demonstrated the heightened sensitivity of IMPT to changes in heterogeneity and motion interplay effects as compared with PS-PT (105-109).

Several methods are available to mitigate these uncertainties: robust beam angle selection utilizing water-equivalent thickness optimization, 4DCT-based robust optimization, layer or volumetric “repainting” delivery, spot-sequence delivery optimization, increased fractionation, spot-size modulation, mini-ridge filter utilization, and respiratory gating or breath-hold-based treatment, to name a few (105,110-114). Unfortunately, most of these methods require additional treatment planning software and devices or increase time and logistical burden on planning, quality assurance, and treatment delivery.

Dosimetric studies

Multiple dosimetric planning efforts have revealed the theoretical benefits of proton therapy and especially PBS-PT over 3DCRT and IMRT techniques. For example, planning comparisons in patients with stage I disease demonstrated reductions in mean dose to ipsilateral lung, total lung, heart, esophagus, and spinal cord for proton therapy over 3DCRT (115). Important dosimetric surrogates for pulmonary complications (V5 and V20) were also substantially reduced. Additional work from MDACC and the University of Florida has exhibited the potential for PT to reduce dose to other structures of concern, such as the chest wall in SBRT approaches (116,117).

Similar results were demonstrated in the locally advanced setting. In fact, proton therapy has shown the potential for targeting more comprehensive volumes, including prophylactic treatment of at-risk nodal volumes, with persistently reduced dosimetric markers for complication when compared with photon approaches (117,118). Another approach being evaluated is photon-SBRT with proton mediastinal nodal irradiation (119). These data also encouraged investigators to compare dose-escalated proton planning with 3DCRT and IMRT in both early- and late-stage disease (120,121). In stage I tumors, dose was escalated from 66 Gy to 87.5 CGE without increases in lung V5, V10, or V20 (121). Similarly, in stage III tumors,

74 CGE was achieved versus 63 Gy with 3DCRT, again without worsening of lung dosimetric constraints (121). Spinal cord, heart, esophageal, and integral doses were also all improved with proton therapy. IMPT has shown a particular ability to reduce projected complication rates in early-stage, late-stage, and postoperative patients with lung cancer. As a result, dosimetric studies for dose escalation with IMPT have shown great promise over comparative plans with 3DCRT, IMRT, and PS-PT (99,100,118,122).

When compared with photon techniques, proton therapy in general substantially reduces moderate-to-low-dose exposure of normal lung and nearby critical tissues when targeting lung cancers. Conformality of high-dose regions, however, is compromised due to the increased uncertainty that results from a combination of highly heterogeneous beam paths in the thorax and the finite range of the proton beams. Mitigation of these uncertainties necessitates motion-robust planning approaches that inherently degrade the high-dose conformality. However, the resulting improvements in dosimetric surrogates for complication from photon experiences would seem to allow for further target dose escalation without increasing toxicity.

Clinical outcomes

Numerous clinical trials have been initiated to investigate proton therapy in lung cancer patients; however, initial results have been mixed. A phase I trial performed at MDACC demonstrated in 25 patients the potential for a moderately hypofractionated course (15 fractions of 3–4 Gy/fraction) of proton therapy without concurrent chemotherapy (biologic agents allowed) (123). Two high-grade toxicities occurred, including a tracheoesophageal fistula in a patient who also received bevacizumab, as well as a case of radiation pneumonitis. A Japanese study escalated dose in stage IA and IB patients to 70–94 CGE (3.5–4.9 CGE/fraction) in 37 patients (124). The authors demonstrated excellent local control and low rates of toxicity. Specifically, they achieved 80% local control and 84% survival at 2 years, with only 6 patients experiencing grade 2 and 3 (3 patients each) pulmonary toxicities. Of these 6, 5 patients had stage IB disease, highlighting the significance of the dose-volume effect. Work at Loma Linda University utilizing PS-PT has shown the efficacy and safety of dose escalation from 50 to 70 CGE in 10 fractions in early-stage lung cancers (125,126). They demonstrated

a 4-year OS rate of 51%, and none of the 111 patients required steroid treatment for pneumonitis (125). Further evidence, primarily out of Japan, has strengthened the case for comparable efficacy of proton therapy and photon SBRT, although some high-grade toxicities have been encountered at relatively acceptable rates (125,127,128).

In locally advanced disease, a recent National Cancer Database analysis suggested a possible improvement in OS for stage II and III patients receiving proton therapy compared with photon therapies, however this difference was not significant on propensity-matched analysis (129). Early clinical trials have also been relatively positive. Following the previously cited study at MDACC, Chang *et al.* published the results of a phase II effort investigating concurrent chemoradiotherapy utilizing proton therapy in unresectable stage III NSCLC (130). This study employed a total dose of 74 CGE, similar to the high-dose arm in RTOG 0617 that demonstrated increased complications and worsened survival with photons. In contrast, Chang *et al.* encountered no grade 4 or 5 toxicities. Grade 3 toxicities were limited to 5 patients with dermatitis, 5 with esophagitis, and 1 with pneumonitis out of total 44 patients enrolled. OS and progression-free survival were 86% and 63%, respectively, at 1 year, with only 4 (9.1%) local-only recurrences. Median survival was 29.4 months. A similar study from the University of Florida closed early after enrolling 14 patients but employed 74 to 80 CGE in conventional fractionation in patients with stage III disease (131). Median OS and progression-free survival were 33 and 14 months, respectively, with no acute grade 3 toxicities and only two patients experiencing late grade 3 toxicities (one gastrointestinal, one pulmonary). Another 15-patient effort from the University of Tsukuba demonstrated similar results at the 74-CGE mark (132).

Multiple phase II and III clinical trials have been initiated to compare proton results to those with photons or to further test dose escalation, especially in the setting of concurrent chemotherapy. Recently, Chang *et al.* nicely summarized trials underway or recently completed (133). The only randomized data to date were presented at the 2016 meeting of the American Society for Clinical Oncology. Disappointingly, this MDACC/Massachusetts General Hospital trial failed to demonstrate a reduction in toxicity with PS-PT versus IMRT, despite relatively similar outcomes (134). It is notable that target volumes were larger in the proton therapy group ($P=0.071$) and that higher doses were generally prescribed in the proton cohort with higher resultant lung volumes receiving 30 and 80 Gy.

Future directions

Proton therapy, mainly through PS-PT experiences, has demonstrated largely acceptable toxicity rates with similar-to-improved outcomes in several small institutional trials. With rapidly expanding availability, the shift toward PBS-PT techniques, improvements in gating/breath-hold approaches, and the potential for daily volumetric image guidance, great promise remains for the application of proton therapy in early, locally advanced, and recurrent lung cancers. Further evidence and clinical investigation are anticipated.

Conclusions

Technological advances in RT, starting with volumetric imaging, have revolutionized the paradigm for lung cancer treatment. These improvements have allowed development of a variety of techniques that can enhance the therapeutic ratio. Application of these techniques has allowed physicians to reduce toxicity by sparing normal tissue in certain cases and to dose escalate the BED to improve tumor control in others. Clinical validation of these advantages has been demonstrated in the form of IMRT and SBRT, respectively. Emerging technologies, such as highly non-coplanar planning (4π) and PBS, continue to push the boundaries of the therapeutic ratio. And although they have raised new challenges regarding precision of delivery, dosimetric comparisons have been promising and clinical data are eagerly awaited. Finally, these technological advances in radiation therapy are paving the way to safely and effectively expand our multimodality treatment arsenal to integrate burgeoning systemic therapies, including immunotherapy.

Acknowledgements

We would like to thank Nancy Knight, PhD, for editorial review of the manuscript and Sarah Snider, JD, for assistance with preparation of the figures.

Footnote

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

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Cite this article as: Diwanji TP, Mohindra P, Vyfhuis M, Snider JW 3rd, Kalavagunta C, Mossahebi S, Yu J, Feigenberg S, Badiyan SN. Advances in radiotherapy techniques and delivery for non-small cell lung cancer: benefits of intensity-modulated radiation therapy, proton therapy, and stereotactic body radiation therapy. *Transl Lung Cancer Res* 2017;6(2):131-147. doi: 10.21037/tlcr.2017.04.04

Stereotactic ablative radiotherapy for early stage non-small cell lung cancer: a word of caution

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Abstract: Recently published data from pooled randomised trials conclude that stereotactic ablative radiotherapy (SABR) can be considered the treatment of choice in operable lung cancer patients fit for lobectomy. This conclusion comes for comparable 3-year survival and much lower risk of early severe morbidity and mortality. In this editorial comment we discuss the validity of the conclusions due to the prematurity of the survival analysis and to the poor accuracy of patients' staging leading to higher rates of regional relapse in the SABR arm. Besides, therapy-related mortality and morbidity in the pooled cohort is much higher than the internationally accepted standards maybe because surgery was not performed according to the best approaches and procedures currently available. The effectiveness of SABR as the sole therapy for resectable lung cancer is still awaiting for sound evidences. It could be adopted for individual cases only in two situations: (I) the patient does not accept surgical treatment; and (II) in cases where the risk of surgical related mortality is considered to exceed the probability of long-term survival after lung resection. For this, a multidisciplinary team (MDT) assessment, including surgeons and oncologists, is mandatory.

Keywords: Lung cancer; pulmonary resection; radiotherapy

Submitted Sep 03, 2015. Accepted for publication Sep 14, 2015.

doi: 10.3978/j.issn.2218-6751.2015.10.10

View this article at: <http://dx.doi.org/10.3978/j.issn.2218-6751.2015.10.10>

In a recently published issue at the *Lancet Oncology*, the authors reported a pooled analysis of two randomised trials [STARS (NCT02357992) and ROSEL (NCT00687986)] comparing stereotactic ablative radiotherapy (SABR) and lobectomy for operable stage I non-small cell lung cancer (NSCLC) (1).

Although the second was closed prematurely due to slow accrual, the authors conclude that SABR can be considered a treatment option in operable patients fit for lobectomy and that future randomised trials including more cases are warranted. The first conclusion comes from the statistically significant advantage on 3-year overall survival in the SABR-treated pooled cohort (although the difference was significant in the STARS trial alone) and from a higher rate of severe treatment-related complications in the surgical arm. In fact, overall surgical mortality was 4% (1/27) and grade 3-4 treatment-related adverse events were 44% (12/27). These data were compared to 0% mortality and 10% (3/31) grade 3 adverse events in the SABR arm.

Any new therapeutic option offering comparable outcomes at a lower risk for the patient has to be praised and disseminated as much as possible. The only condition for doing so is that therapeutic recommendations have to be supported on strong evidence.

Is survival really comparable?

In the aforementioned publication (1), it is to note that in the SABR series, almost 13% of the cases (4/31) suffered from regional lymph node relapse while in the surgical arm, the rate was only 3.7% (1/27) at 3 years. Higher rate of loco-regional relapse has been also reported by Verstegen *et al.* (2), comparing SABR *vs.* video-assisted thoracic surgery (VATS); these authors also found comparable 3-year survival in surgical and SABRT series.

Higher rates of loco-regional relapse in patients treated with radiotherapy can be justified in part by the superiority of intraoperative surgical staging if compared

to clinical staging by FDG-PET image or invasive procedures. Although the authors underline that clinical staging was accomplished in both trials by image (CT and PET scan) and endobronchial fine-needle aspiration or mediastinoscopy when indicated, it is well known that the accuracy of surgical staging is higher (3-5) allowing for adjuvant therapies in surgically staged N1 or N2 cases. Thus, waiting for 5-year survival data in both trials before recommending non-surgical therapy in early stage NSCLC would be advisable. Furthermore, in the ROSEL study, eight (26%) tumours in the SABR group had unknown histology and one patient without histological diagnosis in the surgical group underwent resection and were found to have benign disease. So the proportion of patients who had NSCLC or benign disease in the SABR group remains unclear. This lack of information could have contributed to an increased survival rate in the SABR group.

As more interim analysis on 3-year survival are reported, there is an increasing feeling that SABR or related techniques are equally effective than surgery for early lung cancer. In a publication from Ricardi *et al.* (6), reporting their results in a series of cases, it is stated that “The results of the present study support the routine use of SABR for stage I NSCLC in a daily practice environment”. Such a kind of statements are lacking enough evidence, especially if the new therapy is intended as a substitute of a historically proven effective treatment for early stage lung cancer.

Reported adverse effects of surgery are higher than the internationally accepted standards

High reported surgical mortality (4%) and grade 3-4 morbidity (44%) in the pooled cohort deserves some comments. According to the last report from the European Society of Thoracic Surgeons Database, the standard surgical mortality after lobectomy for lung cancer, in any pathological stage, in Europe is 2% (7), half the reported mortality in Chang's *et al.* paper (1). Due to the low number of cases in the pooled analysis, these differences are probably not statistically significant but they are clinically relevant especially because only stage I cases, where surgical mortality is highly infrequent, were included in both trials.

Also the high rate of major adverse events after surgical therapy has to be regarded with caution. Among the cases included in the SABR group, only three cases (10%) suffered treatment-related grade 3 adverse events: chest wall pain in three (10%), dyspnoea or cough in two (6%) and fatigue and rib fracture in one case (3%). No patient

experienced treatment-related grade 4 toxic effect. On the contrary, in the surgical group, 12 (44%) patients had grade 3-4 related adverse events. Again from the ESTS Database, the rate of major cardio-pulmonary complications after lobectomy, in any pathological stage, is 17.8% (7). Obviously, the accuracy in recording adverse events in a prospective clinical trial is non-comparable to a multi-institutional database where participation is not mandatory. Nevertheless, the difference seems to be large enough as to be accepted without any criticism.

Standardising surgical procedures is much more difficult if compared to radiotherapy. In both trials surgical approach was either thoracotomy or VATS at surgeon's choice. Out of the 27 patients who received surgery, only five had VATS lobectomies, while 19 cases were approached through thoracotomy (in the rest of the cases the procedure was not completed). The term thoracotomy includes any open approach coming from posterolateral incision sectioning latissimus dorsi and serratus anterior muscles, to axillary mini-thoracotomy; that is, any approach where a rib spreader is used. All these approaches are quite different in terms of inflammatory response (8) and related complications. Lung resection for NSCLC is nowadays usually performed through a mini-invasive approach frequently video-assisted. This approach has been demonstrated to produce less short term and long term complications (9) and being equally effective in terms of survival (10,11). Thus, it seems to be logical, when designing a trial to compare the last available technique in radiotherapy to any surgical treatment, selecting also the least aggressive surgical technique, instead of obsolete approaches, to obtain conclusive results.

In the past we have shown that the majority of the risk of lobectomy depends not on patients' conditions but on the quality of the perioperative care (12). Unfortunately, both trials lack precise information on the type of perioperative care received by the patients. It has to be supposed that in both situations the best available care was offered to the patients but this doesn't guarantee the homogeneity of the pooled series with respect to the most relevant variable influencing immediate patients' outcome.

What does it mean “medically inoperable”?

In some of the recently published papers where SABR or any other modality of radiotherapy is offered as an alternative to lung resection, surgery was not considered because patients were: “medically inoperable” (6,13,14). Nevertheless, the specific reasons for inoperability are not

stated clearly. Obviously, any therapy shortening patient's survival is not indicated.

To our mind, the most accurate recommendations to evaluate patients' functional operability have been published in 2013 by Brunelli *et al.* (15). Shortly, these authors recommend:

- (I) Decision on lung cancer therapy has to be agreed by a multidisciplinary team (MDT);
- (II) Patient's age per se is not a contraindication for surgery;
- (III) Cardiologic consultation is needed after specific cardiac risk scoring for thoracic procedures is calculated;
- (IV) Estimation of postoperative FEV1 and DLCO is mandatory in all cases;
- (V) Exercise tests, starting by low technology ones, have to be indicated in cases with limited estimated postoperative FEV1 and/or DLCO (under 60% of theoretical values for age, sex and height).

Maybe the most important and simplest recommendation regarding therapy for lung cancer is that all therapeutically decisions have to be adopted after discussion in a MDT. MDT management has become the standard of care in some countries, after some advantages to both the patient and the clinicians have been demonstrated (16). In our practice, we noticed a slight decrease in lung resection related mortality after implementing internationally accepted guidelines and MDT agreement before indicating surgical therapy for lung cancer patients (17).

In summary, the effectiveness of SABR as the sole therapy for resectable lung cancer is still awaiting for sound evidences. It could be adopted for individual cases only in two situations: (I) the patient does not accept surgical treatment; and (II) in cases where the risk of surgical related mortality is considered to exceed the probability of long-term survival after lung resection. For this, a MDT assessment, including surgeons and oncologists, is mandatory.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by the Editorial Board Member Ying Liang (Department of

Medical Oncology, Sun Yat-sen University Cancer Center (SYSUCC), Guangzhou, China)

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

Comment on: Chang JY, Senan S, Paul MA, *et al.* Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015;16:630-7.

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Cite this article as: Varela G, Gómez-Hernández MT. Stereotactic ablative radiotherapy for early stage non-small cell lung cancer: a word of caution. *Transl Lung Cancer Res* 2016;5(1):102-105. doi: 10.3978/j.issn.2218-6751.2015.10.10

Cranial irradiation in patients with *EGFR*-mutant non-small cell lung cancer brain metastases

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Abstract: The most effective treatment approach for brain metastases in patients with non-small cell lung cancer (NSCLC) and activating epidermal growth factor receptor (*EGFR*) mutations is a current subject of investigation. Cranial irradiation is the standard treatment for brain metastases, but tyrosine kinase inhibitors (TKIs) such as erlotinib have also activity against brain metastases in this subset of patients. The combination of TKI and radiotherapy is a promising one, but data is lacking to indicate whether this is superior to erlotinib or whole brain radiation therapy (WBRT) alone. Retrospective data suggest that WBRT achieves more durable intracranial control compared to erlotinib alone. Randomized, prospective studies will be necessary to determine whether TKI, cranial irradiation, or both is the optimal initial treatment for brain metastases in *EGFR*-mutant NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (*EGFR*); erlotinib; whole brain radiation therapy (WBRT)

Submitted Dec 11, 2015. Accepted for publication Dec 12, 2015.

doi: 10.3978/j.issn.2218-6751.2016.01.08

View this article at: <http://dx.doi.org/10.3978/j.issn.2218-6751.2016.01.08>

Brain metastases occur in 20% to 40% of patients with non-small cell lung cancer (NSCLC) (1). They are a common cause of morbidity and mortality and their incidence may be increasing (2). Historically, therapeutic options for brain metastases have been limited to local therapies such as whole brain radiation therapy (WBRT), stereotactic radiosurgery, surgery or a combination of the above. Due to concern for inadequate central nervous system (CNS) penetration, chemotherapy has not typically been considered a standard primary treatment for brain metastases. In a multi-institutional retrospective analysis that included 1,833 NSCLC patients with newly diagnosed brain metastases treated with radiation therapy between 1985 and 2007, a median overall survival of seven months (95% CI, 6.5–7.5 months) was reported (3).

It is now well established that NSCLC patients harboring activating epidermal growth factor receptor (*EGFR*) mutations have a different prognosis. Studies examining survival in *EGFR*-mutated patients have shown a more favorable median survival of 15–17 months from

onset of brain metastases (4,5). Based on randomized trials demonstrating improved survival, *EGFR* tyrosine kinase inhibitors (TKIs) have replaced cytotoxic chemotherapy as first-line treatments with patients with metastatic *EGFR*-mutant NSCLC (6,7). However, whether *EGFR*-TKI can enhance or replace cranial irradiation in the initial treatment of brain metastases remains unclear.

In 2013, Welsh *et al.* published the results of a bicentric phase II trial in the *Journal of Clinical Oncology* (8) that examined whether the combination of erlotinib and WBRT would improve median survival in patients with NSCLC brain metastases. Erlotinib is known to possess CNS penetrability (9). In the Welsh study, 40 NSCLC patients with radiographically confirmed brain metastases between 2006 and 2010 received a loading dose of erlotinib (150 mg per day for 6 days), followed by concurrent erlotinib (150 mg per day) with WBRT, followed by maintenance erlotinib (150 mg per day) until disease progression or adverse effects. WBRT was delivered as 30 Gy in 3 Gy fractions for the first 10 patients, then changed to a regimen of 35 Gy in

2.5 Gy fractions given concerns of possible neurotoxicity in two patients. The primary endpoint was to detect an increase in median survival from a historical control of 3.9 to 6.0 months. The authors reported that the combination of erlotinib and WBRT was well tolerated, with no grade 4 or 5 treatment-related toxicity. After median follow-up of 28.5 months, the median survival was 11.8 months, significantly surpassing the target of 6.0 months. Of the 40 patients included in the study, 17 had known EGFR status. Subgroup analysis showed a nonsignificant improvement in median survival (19.1 *vs.* 9.3 months, $P=0.53$) and CNS progression-free survival (12.3 *vs.* 5.2 months, $P=0.74$) in the nine patients with known activating *EGFR* mutations compared to the eight patients with known wild-type *EGFR*.

While this pioneering study demonstrates the safety and promise of administering concurrent erlotinib with WBRT, it does not directly indicate whether concurrent treatment is superior to either treatment alone (or in close succession) for *EGFR*-mutant patients. In preclinical models, overexpression of EGFR is associated with radiation resistance (10) and EGFR signaling blockade sensitizes *EGFR*-mutant cells to radiation (11). The investigators of the trial hypothesized that concurrent EGFR inhibition and WBRT may therefore be synergistic and potentially improve survival. However, the single-arm design of the study and the limited number of patients with known *EGFR* mutations leaves open the question of whether combination therapy would have been any more effective than erlotinib or WBRT alone. Though the study cohort's survival handily exceeded the historical expectation of 3.9 months, some of this could have been attributable to general improvements in the prognosis of NSCLC patients with brain metastases, due to factors such as stage migration from the widespread use of brain MRI screening. Known *EGFR*-mutant patients had particularly favorable results, but such patients are now known to have relatively better prognosis when treated with erlotinib alone.

There is prospective evidence that EGFR-TKIs are an effective primary treatment for *EGFR*-mutated NSCLC brain metastases. In an open-label, single institution phase II study, 28 molecularly selected patients with activating *EGFR*-mutant NSCLC and brain metastases received either oral gefitinib (250 mg daily) or erlotinib (150 mg daily) (5). Study patients did not receive prior local therapy for brain metastases such as radiation or surgery. The median survival and CNS progression-free-survival was 15.9 and 6.6 months, respectively. In another phase II trial, 40 patients

with non-molecularly-selected NSCLC and asymptomatic brain metastases were treated with erlotinib (150 mg daily). Clinically significant improvement in OS was observed in activating *EGFR* mutation-positive patients (37.5 months, $n=8$) compared to *EGFR* wild-type patients (18.4 months, $n=15$; $P=0.14$), as well as in CNS progression-free survival (15.2 *vs.* 4.4 months, $P=0.02$). These studies not only corroborate the longer survival observed for patients with *EGFR*-mutant NSCLC and brain metastases reported by Welsh *et al.*, they also suggest that erlotinib monotherapy may be an effective primary treatment for patients with *EGFR*-mutant NSCLC brain metastases.

There is no randomized data directly comparing erlotinib to WBRT for primary treatment of *EGFR*-mutant NSCLC brain metastases. In a retrospective analysis, our group examined the role of cranial irradiation in patients with *EGFR*-mutant lung adenocarcinoma and newly diagnosed brain metastases (12). While it did not reach statistical significance, we observed longer survival in patients who received WBRT ($n=32$, 35 months) compared to patients who received erlotinib alone ($n=63$, 26 months, $P=0.62$) for newly diagnosed brain metastases. Our results corroborate the favorable survivals reported by Welsh *et al.*, as well as the phase II studies of primary EGFR-TKI therapy for brain metastases discussed above. Furthermore, we found that patients who received WBRT had significantly longer time to intracranial progression compared to those who received erlotinib alone (24 *vs.* 16 months, $P=0.04$), despite having significantly greater intracranial disease burden (more patients with >3 brain metastases and larger lesions received WBRT). This study suggests that WBRT retains an important role in intracranial control in patients with *EGFR*-mutant NSCLC brain metastases. In a recent meta-analysis that included 12 non-comparative studies and 363 patients, upfront cranial radiation was found to improve intracranial disease control and survival outcomes compared to TKI alone (13). The majority of patients included in the study received TKI alone ($n=185$), 115 patients received WBRT alone, 23 patients received stereotactic radiosurgery alone, and 40 patients received concurrent WBRT and TKI. Despite significant methodological limitations, this analysis further highlights the notion that upfront radiotherapy should not be summarily abandoned in *EGFR*-mutant NSCLC patients even though targeted therapies have also demonstrated CNS activity.

Pre-clinical data has demonstrated that erlotinib can cause radiosensitization through cell cycle redistribution, induction of apoptosis, and inhibition of DNA repair (11). It

is therefore reasonable to hypothesize that the combination of erlotinib and WBRT for *EGFR*-mutant NSCLC would result in significantly improved CNS disease control and potentially enhance survival. In a retrospective analysis, Gow *et al.* demonstrated that patients with *EGFR* mutations had higher response rates to WBRT compared to patients with wild-type *EGFR* disease. The administration of *EGFR*-TKI during WBRT was independently associated with response to WBRT, and response to WBRT was an independent predictor for survival (14). In a second study, concomitant administration of gefitinib and WBRT was found to result in higher treatment response and disease control rates in patients with *EGFR*-mutant NSCLC brain metastases compared to gefitinib alone (15). In 2014, Lee *et al.* reported results of a multicenter trial that included 80 non-molecularly selected NSCLC patients with newly diagnosed brain metastases randomized to WBRT alone (20 Gy in 5 fractions) or WBRT with concurrent erlotinib (16). They reported median survival of 2.9 months with WBRT alone and 3.4 months with WBRT plus erlotinib. However, only one patient had known activating *EGFR*-mutation status, limiting the study's relevance to current practice where *EGFR* mutation status is routinely verified, and erlotinib is only offered to patients with activating mutations. Overall, these studies suggest that the approach of concurrent *EGFR*-TKI and WBRT is a promising treatment deserving further study in patients with brain metastases and *EGFR* mutations. However, definitive support for this strategy is limited by the dearth of prospective randomized data, and the fact that many published studies only contained a small subset of patients with known *EGFR* mutations.

In summary, the phase II study of concurrent erlotinib and WBRT from Welsh *et al.* demonstrates the tolerability and safety of the combination in treating newly diagnosed brain metastases from NSCLC. Patients with *EGFR*-mutated NSCLC brain metastases appear to have improved intracranial disease control and survival compared to patients with *EGFR* wild-type disease. Nevertheless, whether erlotinib, radiotherapy, or both is the optimal treatment for brain metastases in this population remains unanswered. Retrospective studies (12-14) indicate that upfront cranial irradiation may improve intracranial control and possibly survival compared to *EGFR*-TKI alone, and the combination of WBRT and *EGFR*-TKI may ultimately prove to be the best strategy (14,15). However, this needs to be confirmed with prospective randomized trials, one of which is ongoing: the TRACTS trial is comparing concurrent erlotinib and WBRT *vs.* erlotinib

alone (clinicaltrials.gov/NCT01763385). Crucially, this trial limits eligibility to patients with known activating *EGFR* mutations. Until such data are available, we suggest that patients with brain metastases from *EGFR*-mutant NSCLC should still be considered for upfront cranial irradiation, prior to or concurrent with erlotinib or other targeted therapies.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Commentary commissioned by Guest Editor Hongcheng Zhu, MD, PhD (Department of Radiation Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

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

Comment on: Welsh JW, Komaki R, Amini A, *et al.* Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. *J Clin Oncol* 2013;31:895-902.

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Cite this article as: Yang TJ, Wu AJ. Cranial irradiation in patients with *EGFR*-mutant non-small-cell lung cancer brain metastases. *Transl Lung Cancer Res* 2016;5(1):134-137. doi: 10.3978/j.issn.2218-6751.2016.01.08

Advances in palliative radiotherapy of metastatic non-small cell lung cancer

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Abstract: Radiotherapy has important role in the palliation of metastatic non-small cell lung cancer (NSCLC). Randomized trials tend to suggest that, in general, short regimens give similar palliation though with more long term toxicity compared to longer regimens. Hypofractionated radiotherapy has been the standard of care for the palliative management of lung cancer since decades. Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) are forms of extreme hypofractionation being used more frequently in the treatment of single or oligometastases. In general, they offer good tumor control with little toxicity (at a more expensive cost) compared to the traditionally fractionated radiotherapy regimens. The combination of targeted therapy with radiotherapy is an evolving concept in the management of metastatic lung cancer.

Keywords: Non-small cell lung cancer (NSCLC); hypofractionation; molecular targeted therapy; palliative care; radiosurgery

Submitted Jun 16, 2015. Accepted for publication Jul 30, 2015.

doi: 10.3978/j.issn.2218-676X.2015.08.02

View this article at: <http://dx.doi.org/10.3978/j.issn.2218-676X.2015.08.02>

Introduction

Patients with metastatic lung cancer have a poor prognosis and the therapeutic options are limited. Controlling their symptoms and maintaining their quality of life should be the principle of treatment. The primary goal of treatment is to use the most effective and the least toxic regimen for the treatment. Radiotherapy has largely been used to palliate non-small cell lung cancer (NSCLC) for this reason (1). Multiple prospective randomized trials using different dose or fractionation schedules have shown that palliative radiotherapy alleviate thoracic and extra-thoracic symptoms in patients with locally advanced or metastatic NSCLC (1-3). Indications for thoracic radiation include hemoptysis, cough, chest pain, dyspnea, obstructive pneumonia, superior vena cava syndrome and hoarseness of voice. Indications for extra-thoracic radiation therapy were initially limited to brain and bone

but has now widened to include adrenal abdominal lymph nodal, liver and re-irradiation for spinal metastases. In a comprehensive review by the Cochrane Collaboration (4), no significant difference among short compared to long radiotherapy regimens in terms of palliation and hypofractionated radiotherapy is the standard of care. The clinical picture and the performance status of the patients must dictate the treatment regimen. Short course and simple treatments must be generally preferred. Our typical palliative dose is 8 Gy in single fraction or 30 Gy in 10 fractions which is simple, well tolerated, efficient and comparable to other regimens (5,6).

Advances in palliative radiotherapy of NSCLC

‘Oligometastatic disease’ is a disease state intermediate between localized disease and metastatic disease (7) where

local treatment modalities have a role in reducing tumour burden and improving the long term survival. Surgery and stereotactic body radiation therapy (SBRT) are the competing modalities; and it is being increasingly recognized that SBRT can provide results equivalent to surgery while being non-invasive and producing minimal complication rates (8). Among the sites favored for the local therapy for oligometastatic tumours are the liver, lung, spine and the adrenal glands. The volume and number of sites of oligometastatic disease are vital in the decision making for aggressive local therapy and affect survival outcomes. Also of increased interest in recent times is the evolving role of reirradiation to metastatic sites to achieve better quality of life (9,10).

SBRT for thoracic disease

SBRT or “stereotactic ablative radiotherapy” is a form of extreme hypofractionated radiation delivery. It utilizes hypofractionated precisely targeted high dose radiation to the tumor while minimizing radiation to adjacent normal tissue.

Stereotactic radiosurgery (SRS) for the lung became possible because of the advent of 3D treatment planning and body immobilization devices to reduce intra- and inter-treatment movement of the tumour. It involves the use of 4DCT scans to manage the pulmonary motion during treatments. This technique allows treatment of small to moderate sized tumors, in either single or limited number of high daily dose fractions, with high chances of local control and little toxicity. Anti-tumour effects of extreme hypofractionation may be due to reasons beyond direct ionizing radiation induced DNA damage such as damage to the tumour vasculature, tumour stroma (11) and enhancement of tumour specific adaptive immune response (12). Clinically the expected results of hypofractionation have clearly overshoot the expected efficacy with hypofractionation as arrived by radiobiological models particularly the LQ model. The role of hypofractionation in lung has been established due to improvement in the therapeutic ratio as the α/β ratio of the tumour is high compared to the α/β ratio of the surrounding lung parenchyma which is relatively higher. Also the fact that the peripheral part of the lung behaves as a parallel organ may be helpful in delivery of high doses per fraction in the treatment of lung tumours. Hypofractionated radiotherapy has shown benefit in clinical trials in the radical treatment of lung cancer (13,14). Even in the setting of highly conformal setting of SBRT, the mean lung dose (>4 Gy) and the volume receiving 20 Gy

($V_{20}>4\%$) has shown maximum correlation with radiation pneumonitis (15). This by itself shows the thin line between control and toxicity in a radiosensitive tissue like lung thus emphasizing the role of SBRT. SBRT also has a role in treating selected patients with painful bone metastases or with oligometastases in, liver spine and adrenals. The COMET study (stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors) (SABR-COMET) is a randomized Phase II Trial open in Europe and Canada, comparing patients with up to five metastatic lesions from any primary tumor site who can receive SABR. Eligible patients are randomized to either standard palliative radiotherapy versus SABR (16).

SBRT for liver oligometastasis

The incidence of metastasis to the liver is in the range of 30-70% of patients with metastatic lung cancer and a subset (10-15%) of patients have been shown to have oligometastatic disease in the liver. There has been gaining interest in surgical or non-surgical treatment of liver oligometastasis (17). Ercolani *et al.* have shown in their case series of survival of as high as 3 years (in one out of three patients) after surgical resection of oligometastatic disease to the liver (18). When radiation is used in the treatment of oligometastasis to the liver, it has been shown that the complication probabilities steeply rise with small increases in the dose. For a dose of 60 Gy delivered in three fractions by SBRT, it is recommended that <700 cc of the normal liver receive >15 Gy (19,20). This calls for accurate and conformal therapies.

SBRT in brain metastases

When brain metastases occur in patients with NSCLC, there is often active disease at the primary site or elsewhere in the body. In few cases, the brain is the only site with active disease (21). There are many guidelines on the treatment of brain metastases showing that therapeutic intervention (radiotherapy or surgery) is associated with improved control of disease in the brain (22).

SRS to the brain involves a single shot of high dose radiotherapy and can control very efficiently one to few metastases either close to the surface or deep in the brain (23). No randomized trials have compared SRS with traditional surgical resection. The traditional whole brain radiotherapy (WBRT) treats the metastases and may also prevent the growth of new metastases, but may

cause side effects such as memory loss. Recent Cochrane review shows that there is low quality evidence that adding upfront WBRT to surgery or to SRS decreases any intracranial disease progression at 1 year. There is also no clear evidence of an effect on overall survival and progression free survival (24). However a phase III trial comparing WBRT and stereotactic boost treatment showed improved functional autonomy performance status for all patients and survival for patients with a single unresectable brain metastasis. WBRT and stereotactic radiosurgery has been as a standard treatment for patients with a surgically unresectable oligometastasis (25).

SRS has become increasingly important treatment technique in the management of brain metastases, but it is not available everywhere and it is more expensive than WBRT. An approach of SRS alone as initial treatment of brain metastases has allowed patients to delay or avoid WBRT and its associated side effects (26). The benefit of SRS in resource poor settings and the cost-benefit ratio is yet to be defined.

Adrenal metastasis

Metastatic disease from a NSCLC to the adrenal gland is common, and systemic treatment is the therapeutic option of choice. However patients with isolated adrenal metastasis have shown good response after surgical resection. The non-invasive option is SBRT (27) which has shown markedly improved progression free survival times and modest improvement in overall survival (28).

Spinal lesions

Durable pain control is one of the primary goals for metastatic spinal lesions which can be achieved by sustained local control. It has been shown that the local control is gradually lost over a period of time after conventional radiotherapy to spinal metastasis (6,29). This lays the foundation for dose escalation for durable pain relief with SBRT by delivery of higher biologically equivalent dose at the time of initial irradiation. Also in re-irradiation of metastases, the margin for error is very small due to the low tolerance of the spinal cord (30). Significant reductions in patient-reported pain and other symptoms were evident 6 months after SBRT, along with satisfactory progression-free survival and no late spinal cord toxicities (31). Radiation Therapy Oncology Group (RTOG) study number 0631 is an open Phase II/III Study of Image-Guided SBRT for

localized spine metastasis comparing one treatment of 16 Gy delivered with SBRT versus a single fraction of 8 Gy.

Targeted therapy with palliative radiotherapy

When used in combination with radiotherapy, molecularly targeted agents aim to increase the effect of the radiation on the tumor. Substantial preclinical data have accumulated to show that these agents can potentially enhance the tumor response to radiotherapy through a variety of mechanisms (32). They offer new but challenging possibilities for clinical practice. There is a growing evidence for combination of radiotherapy and targeted therapies in other cancers (e.g., head and neck cancers) (33,34). However the addition of targeted agents to thoracic radiation so far has not improved outcomes in patients with locally advanced NSCLC (35,36).

The combination of radiotherapy and molecular agents targeting vascular endothelial growth factor (VEGF) mediated angiogenesis may result in synergistic effects leading to enhanced tumor cell killing on the one hand, but to enhanced normal tissue damage on the other hand (37). To date, there are only limited data on the efficacy and toxicity of anti-angiogenic agents given in combination with radiotherapy in lung cancer. Given the strong preclinical rationale for combining Epidermal Growth Factor Inhibitor inhibitors (Cetuximab, Panitumumab, Erlotinib, Gefitinib, Lapatinib, and Trastuzumab) with radiation, additional studies are needed. Phase I/II data and lack of long-term experience suggest that physicians should consider combined modality approaches with caution, considering the possibility of uncommon but potentially severe toxicity (38). With high-precision irradiation techniques (such as SBRT), the combination with targeted agents is feasible with apparent no increase in severe adverse events. Phase III trials involving addition of erlotinib or Temozolomide to radiosensitize WBRT failed to show any benefit (39). In another trial which attempted to substitute erlotinib for WBRT showed that the incidence of intracranial failures was high in the erlotinib arm (40) suggesting that targeted therapies can never substitute for WBRT in NSCLC with brain metastasis. Nevertheless, the addition of molecular targeted drugs to radiotherapy outside of approved regimens or clinical trials warrants careful consideration on a case by case basis.

There is still a debate on the timing of combining targeted agents with radiation and is an open area for future research.

It cannot be assumed that giving the drug concurrently with radiation (as it happens with chemotherapy) is always the optimal treatment strategy. Indeed, drugs that cause cell cycle arrest or prolong cells in the radio-resistant phase of the cell cycle may jeopardize the radiation effect (34).

Brachytherapy

High dose rate (HDR) endobronchial brachytherapy for palliation of hemoptysis or obstruction as these sites are not amenable to ablation by stereotactic techniques (using doses between 6 and 10 Gy at 1 cm). Hypofractionation is the underlying principle in this setting also. However this is not in common use the rarity of the clinical picture meriting brachytherapy. External radiation alone is more effective than endobronchial brachytherapy for symptom palliation in previously untreated patients with endobronchial NSCLC. Endo-bronchial therapy is recommended for symptomatic patients with recurrent endobronchial obstruction previously treated by radiation, provided it is technically feasible (41).

Cost benefit ratio in SBRT

The basic principle of palliative case is to do best with as little as possible. Though these advanced techniques offer conformal and accurate doses with adequate palliation of symptoms and better quality of life, they have to be evaluated in terms of increased costs associated with the treatment particularly in developing countries where the patient himself bears the cost of the treatment. Cost effective analysis from various trials comparing SBRT with other treatment modalities showed that the treatment outcomes are comparable or superior compared to other treatment modalities and are cost effective in the long run (42). SBRT compared to other modalities was more effective in freeing up hospital resources and allowing patients to resume normal activities earlier thus minimizing indirect costs (43,44).

Conclusions

With the newer advancements in radiation delivery techniques allowing a very high precise radiation dose to a well localized target, there is a wealth of data for the practice of evidence based medicine in the palliative management of lung cancer. Advocating aggressive management of oligometastatic disease offers the potential for enhanced

quality and quantity of survival. This has not only widened the scope of palliative radiation in the metastatic setting as well as re-irradiation of previously treated sites.

Acknowledgements

None.

Footnote

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

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Cite this article as: Kapoor R, Simha V. Advances in palliative radiotherapy of metastatic non-small cell lung cancer. *Transl Cancer Res* 2015;4(4):397-402. doi: 10.3978/j.issn.2218-676X.2015.08.02

Can proton beam therapy be clinically relevant for the management of lung cancer?

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: H Giap; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Lung cancer is the leading cause of cancer death in the USA and worldwide. Radiation has played a significant role in the treatment of all types and stages of lung cancer. Despite improvement in lung cancer treatment over the past few decades, the mortality and treatment morbidities for lung cancer patients remain high. Lung cancer treatment often requires multi-modality approaches. Radiation therapy (RT) for lung cancer is challenging due to pre-existing morbidity, poor lung tolerance and its location near by critical organs (heart, esophagus, spinal cord). Conventional RT with photon has improved, but has reached a plateau. Particle beam therapy is promising due to the ability to spare normal surrounding tissues from unnecessary collateral radiation. Particle beam therapy has been used in the past decade in USA and Japan with encouraging results. This article will review the basic physics and radiobiology of particle beam therapy and their role in the management of early stage, locally advanced, and recurrent lung cancer.

Keywords: Proton therapy; particle beam therapy; lung cancer; intensity modulated proton therapy (IMPT)

Submitted Apr 02, 2015. Accepted for publication May 07, 2015.

doi: 10.3978/j.issn.2218-676X.2015.08.15

View this article at: <http://dx.doi.org/10.3978/j.issn.2218-676X.2015.08.15>

Introduction

Lung cancer is the leading cause of cancer death in the United States and worldwide (1). According to the American Cancer Society, there were 221,200 new cases and an estimated 158,040 deaths in the USA in 2015. Mortality for lung cancer is higher than prostate, breast, colorectal, and pancreatic cancers combined. Local control (LC) is important for lung cancer. Failure to control local disease in the thorax accounts for 2/3 of deaths for lung cancer.

In terms of treatment, lung cancer has been divided into two major histologic types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). According to SEER data, SCLC accounts for 10-15% of all lung cancer, and they are typically treated by systemic therapy. The rest are NSCLC, which have an overall prognosis of 15% 5-year survival. Lung cancer survival significantly decreases with later staging (SEER). Early stages IA and IB have 49% and

45% 5-year survival, respectively. Stage IIA and IIB have about 30% 5-year survival. However, there is sharp decline in survival from stages IIIA (14%) to IIIB (5%) to IV (1%). Treatment guidelines have been developed by the National Cancer Care Network (NCCN) depending on the stage of the disease at presentation.

Local disease is the major cause of symptoms in lung cancer patients. Radiation therapy (RT) plays a role in almost all stages of lung cancer. For stage I NSCLC, surgery alone is recommended for medically operable tumors. Alternatively, RT is used as a sole modality to treat stage I NSCLC for patients who are medically inoperable or refuse surgery. In stage II-III NSCLC, radiation is used in combination with systemic therapy (chemotherapy and/or targeted therapy) and sometimes surgery to provide definitive treatment. Radiation is also used in limited stage SCLC in combination with systemic therapy for curative

treatment. RT is the most effective treatment for palliation for stage IV lung cancer (2).

Treatment of lung cancer is challenging due to: (I) most patients are diagnosed at late stages III or IV; (II) most lung patients are elderly (2/3 patients are 65 years old or older) and often have co-morbidities; (III) current treatments for lung cancer are difficult to tolerate since they require radical surgery and/or combined systemic cytotoxic drugs and radiation to the above organs; (IV) lung cancers are radiation-resistant and surrounded by healthy lung tissues, which are radiation sensitive. Furthermore, lung tumors are often located near other critical organs such as the heart, esophagus, and spinal cord. Too much radiation to the lung can cause radiation pneumonitis, which can decrease lung function, require long term steroid and oxygen, and sometimes cause death. The risk of radiation pneumonitis is dependent on both irradiated volume and dose. Radiation esophagitis can cause pain and difficulty with swallowing, hence causing weight loss. Sometimes, it can cause ulceration and stenosis as late side effects. Too much radiation to the heart can lead to major cardiac adverse events such as myocardial infarction, pericarditis, etc. Similar to the lung, the risk of complication to the heart and esophagus is both dose and volume dependent.

Thus, any improvements to lung cancer radiation treatment would ideally increase dose to the tumor and/or decrease dose to surrounding healthy tissues. Because of the Bragg peak effect, particle beam treatment has unique physical properties that allow RT to be delivered with less normal tissue exposure compared with photon-based RT (3); hence, lung cancer is a perfect application for particle beam therapy for these reasons. In this article, the role of proton beam therapy (PBT) in lung cancer is explored in three scenarios: (I) early stage lung cancer; (II) locally advanced lung cancer; (III) recurrent lung cancer.

Physics and radiobiology of proton beam therapy

Starting in the mid 1950's, over 130,000 patients have undergone particle beam treatments, of which, about 110,000 are proton and the rest are light ions such as carbon and helium. Traditionally, the therapeutic use of charged particles is motivated primarily by their inverted depth-dose profile from the Bragg peak; thus, the collateral damage induced in healthy tissues surrounding the tumor is limited. Distinct beams of different energies can then be integrated to achieve the prescribed dose in a region as large as the target volume, resulting in the production of

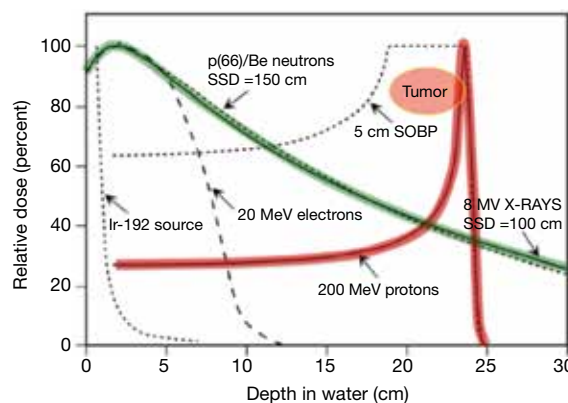


Figure 1 Schematic of dose distribution along a single line for proton versus other types of radiation. The Bragg peak and SOBP are demonstrated. SOBP, spread-out Bragg peak; SSD, source-to-skin.

what is designated as the spread-out Bragg peak (SOBP) (4) (Figure 1). A proton is produced by removing the orbiting electron from the hydrogen atom, resulting in a positively charged hydrogen ion. These ions are further accelerated to a typical energy of 70-250 mega electron-volts (MeV) in an accelerator such as synchrotron, or cyclotron. These protons are then delivered to a patient precisely to the appropriate depth in the body through either a “passive scattering” or “beam scanning” technique (5). Protons can be delivered with two different radiation techniques: passive scattering proton therapy (PSPT) or pencil beam scanning technique (PBS). In PSPT, the tumor volume is irradiated as a whole, using collimators and compensators for dose conformity. With PBS, the target volume is scanned spot-by-spot with a narrow proton beam, sequential targeting of 300 to 600 spots in a voxel-like array, enabling intensity-modulated proton therapy (IMPT) (6,7).

Charged particles such as protons have minimal ionization along their beam path, the dose delivered to any point along the path is minimal, and the entrance dose for an individual beam is less than that for a comparable photon beam (8). Consequently, deep-seated tumors, especially those close to organs at risk (OAR), represent an ideal configuration for exploiting the advantageous physical characteristics of charged particle beams (5). Typically, the integral dose delivered to the body can be 2-3 times lower with protons when compared to X-rays delivered by intensity modulated radiation therapy (IMRT) (9). The increased linear energy transfer (LET) compared to X-rays when protons are near the Bragg peak is correlated with

a localized energy deposition and induction of enhanced unreparable biological damage (10). Protons are also different from photon irradiation in terms of killing power. The relative biological effectiveness (RBE) for proton RT is estimated at 1.1 times that for photons. Hence, proton RT has theoretically 10% more cancer kill capability for each gray (Gy) than photon RT (11). As historically described in the literature, this absorbed energy leads to breaks in DNA strands and free radical formation, resulting in cell death predominantly in rapidly reproducing tissue. Tumor response, as we now know, is strongly associated with local microenvironment, communication, and interaction between cancer cells and healthy cells, as well as among targeted and non-targeted cells (12).

A current aspect of discussion is whether the use of a fixed relative biological effectiveness in PBT is still appropriate, or if a variable RBE is more pertinent taking into account the dependency on LET, tissue properties, total dose, and dose fractionation (5). The main benefits of PBT when compared to photon are based on the above mentioned interactions with matter when the particles are traveling in a patient. The fact that the proton beam virtually stops at the target volume results in marginal radiation exposure beyond the tumor, allowing for the sparing of distally placed tissues (13). In contrast, photons travel through the entire body from the entrance to the exit point. This difference in dosage to distal OAR makes proton therapy a more ideal treatment option for tumors surrounded by critical tissues. Maximal sparing of these crucial organs is important in potentially improving patient outcomes (survival, quality of life, and toxicity) (11).

From a genuinely physics point of view, the dose distribution of protons is in most cases superior to that of photons. The lateral dose fall-off or beam penumbra is better than photon at shallow depth, then it becomes worse for protons as the proton beam travels deep into the tissue (14). Several studies demonstrate that PBT allows the delivery of higher tumor doses compared to photons while sparing healthy tissues. The Radiation Oncology Collaborative Comparison consortium performed a planning study for 25 NSCLC, stage IA-IIIB patients. On 4D F18-labeled fluorodeoxyglucose (FDG) positron emission tomography (PET)—computed tomography (CT) scans, the gross tumor, clinical and planning target volumes, and OAR were delineated and it was illustrated that passive scatter proton therapy resulted in the lowest dose to the OARs, while keeping the dose to the target at 70 Gy. The integral dose was higher for 3D-Conformal RT (CRT)

(59%) and IMRT (43%) than for PSPT. The mean lung dose was 18.9 Gy for 3D-CRT, 16.4 Gy for IMRT, and 13.5 Gy for PSPT (15). Chang *et al.* completed a planning study comparing 3D-CRT, IMRT, and PSPT in 25 patients with stage I-III NSCLC. Using photons, the mean tumor dose of 63 Gy and the mean V20 (lung) was 34.8%, compared to a mean proton dose of 74 cobalt gray equivalent (CGE) to the tumor and a mean V20 (lung) of 31.6%. The authors concluded that proton treatment appears to reduce dose to normal tissues significantly, even with dose escalation, compared with standard-dose photon therapy, either 3D-CRT or IMRT (16). In stage I NSCLC, protons also achieved lower doses to OARs than photon stereotactic body radiation therapy (SBRT) (17).

It is essential to recognize that range uncertainties, or uncertainty regarding where the proximal and distal edges of the Bragg peak will be in the patient, are a perilous component to proton therapy planning (18,19). In hypodense tissues, where beam attenuation is low (e.g., lung), this consideration carries a major importance, especially at the most distal part of the SOBP. Because of organ motion as well as changes in lung density during respiration, PBT in the lung requires significantly more effort in planning and dose validation (2).

Proton therapy for early stage lung cancer

SBRT surface has been found to be as effective as surgery in regards to primary tumor control rates and overall survival (OS) for patients who refuse surgery or with medically inoperable early-stage lung cancer (20-22).

Since 1999 studies have reported an 80 to 90 percent rate of LC for patients with stage I NSCLC treated with hypofractionated proton beam radiotherapy (23-27). Supporting the idea that a higher dose can result in better tumor control, dose escalation has been actively studied in the past two decades. These clinical investigations confirmed a dose-response relationship both in terms of LC and OS duration (28).

Bush *et al.* reported phase I-II study from Loma Linda University for a group of 111 patients with NSCLC stage T1-2 N0 using a 2-week course of hypofractionated proton therapy for 60-70 Gy in 10 treatments with tolerable side effect and good LC (about 75% for T2 patients at 4 years), no grade 3 pneumonitis, or change in FEV1 or DLCO function. There were four patients with rib fractures (tumor abutting the chest wall).

The range uncertainties were studied and compared

Table 1 Advantages and disadvantages of using protons and photons for stereotactic body radiation therapy (SBRT).

	Advantages	Disadvantages
Photons	<ul style="list-style-type: none"> • Heterogeneous dose within tumor can be used for hypoxic centers • Arc therapy can spread out exit dose • depth-dose profile minimally affected 	<ul style="list-style-type: none"> • Higher exit dose • Scattered dose • Increased risk of second malignancy • Relatively high entrance dose
Protons	<ul style="list-style-type: none"> • Relatively low entrance dose • Maximum dose at depth • No exit dose • Reduction in integral dose • Homogeneous dose reducing hotspots within tumor 	<ul style="list-style-type: none"> • Very sensitive to tumor motion or tumor shrinking • Range uncertainties • Variation in patient anatomy anywhere in the beam path can lead to severe degradation of the actual delivered dose

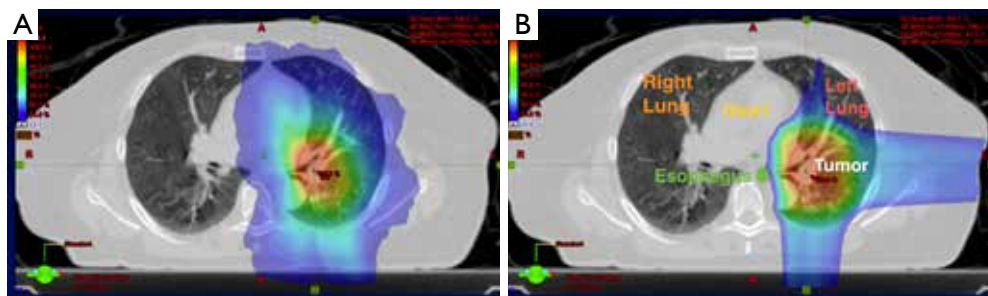


Figure 2 Comparative dosimetry for photon (A) versus proton (B). At the high dose region near the tumor, the photon IMRT plan is more conformal than the proton plan due to added margin for range uncertainty for proton. At the low dose region, there is more sparing of the normal structures (heart, lung, esophagus, and spinal cord). IMRT, intensity modulated radiation therapy.

the use of protons and photons for SBRT for NSCLC by Seco *et al.* (29). The authors attempted an overview of the advantages and disadvantages of the usage of this different particles reproduced in *Table 1*.

This concept is demonstrated in *Figure 2*, which shows the comparative dosimetry with photon plan on the left and proton plan on the right. The photon plan has higher dose conformity at the high dose region near the tumor due to range uncertainty while the proton plan can spare much better at the low dose region. An example of an actual patient is shown in *Figure 3*.

Some authors explored dose escalation with SBRT using proton. Onishi *et al.* found that among different SBRT regimens, a biologically effective dose (BED) of at least 100 Gy is associated with a higher 5-year LC rate (91.9% *vs.* 73.6%) and longer OS (88.4% *vs.* 69.4%) than a BED of less than 100 Gy (30). Bush *et al.* reported treatment dose escalated from 51 to 70 CGE in 10 fractions for 111 patients (T1/T2) (4). LC and survival were well-established to improve with escalated doses. OS at 5 years

was 18%, 32%, and 51% at 51 CGE, 60 CGE, and 70 CGE. Nonetheless, tumors greater than 5 cm were associated with worse LC. There were no cases of radiation pneumonitis, suggesting room for increased dose delivery to improve outcomes (3). Nihei *et al.*, reported treatment dose between 70-94 CGE in 20 fractions for 37 patients (T1/T2 <5 cm) (25). Two-year LC and survival were 98% and 84%, respectively. Late pulmonary toxicity was associated with tumor shrinkage during treatment, demonstrating the need for adaptive replanning (31). Recently, Makita *et al.* (24) explored toxicities and prognostic factors related to two high-dose PBT protocols (BED ≥ 100 Gy) for treatment of stage I NSCLC. Patients (n=32) with peripherally located tumors were given 66 Gy (RBE) over 10 fractions while patients (n=24) with centrally located tumors were given 80 Gy (RBE) over 25 fractions. The three-year OS, progression-free survival (PFS), LC rates were 81.3%, 73.4%, and 96.0%, respectively.

The authors concluded that both high-dose PBT protocols achieved high LC rates with tolerable toxicities

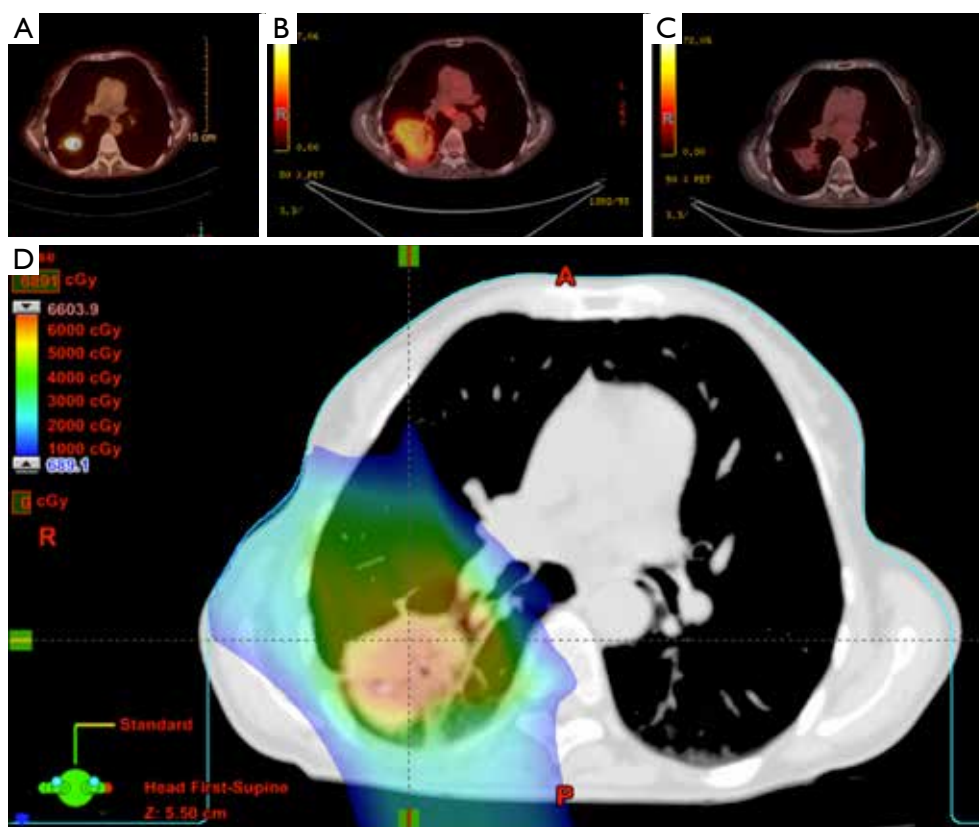


Figure 3 Intensity modulation proton therapy (IMPT) was used to treat this early stage non-small cell lung cancer (NSCLC), stage T2 N0 M0, with 65 Gy in 10 fractions, using a posterior and right anterior oblique field. The PET/CT images below showed tumor prior to treatment (A), at 2 months after treatment (B), and 10 months after the treatment (D). The PET/CT image taken at 2 months (B) showed the inflammation in the treated area and a reactive lymph node in the mediastinum. PET, positron emission tomography.

and that the standardized uptake value was a significant prognostic factor.

At Scripps Proton Therapy Center, patient is set-up in supine position with both arms above the head and immobilized with a vacuum bag and head holder *Figure 4*. 4D CT scan was done using Varian RPM system to evaluate tumor motion. If the tumor motion is 1 cm or less, then the ITV approach was done. The GTV was contoured on lung window on inspiration and expiration phases, GTV was expanded with 5 mm margin for CTV (excluding chest wall or bronchus). The two CTV are combined to form ITV. Setup uncertainty (5 mm) and range uncertainty are added to form beam specific PTV as shown in *Figure 4*. Typically, two fields are used to treat the tumor daily, and orthogonal kV images were obtained for each field prior to the treatment.

For patients with tumor more than 1 cm, then we use the deep inspiration breath hold (DIBH) technique with

the SDX Spirometric Motion Management System (QFix, Avondale, PA, USA) as shown in *Figure 5*. The system consists of a spirometric breathing device, goggle, and a computer system. The system allows patients to voluntarily hold their breath at a set level with the visual feedback.

Figure 6 showed a case of early stage lung cancer that was treated using the SDX system to mitigate the tumor motion. Intensity modulation proton therapy (IMPT) was used to treat this early stage non-small cell lung cancer (NSCLC) with 70 Gy in 10 fractions. Two posterior fields were used. Tumor motion was minimized using the SDX system. The panels below showed the PET/CT images before (A) and 8 months after treatment (B).

Proton therapy for locally advanced lung cancer

Stage II/III NSCLC are treated with combination of chemotherapy and RT. Median survival for stage II/III

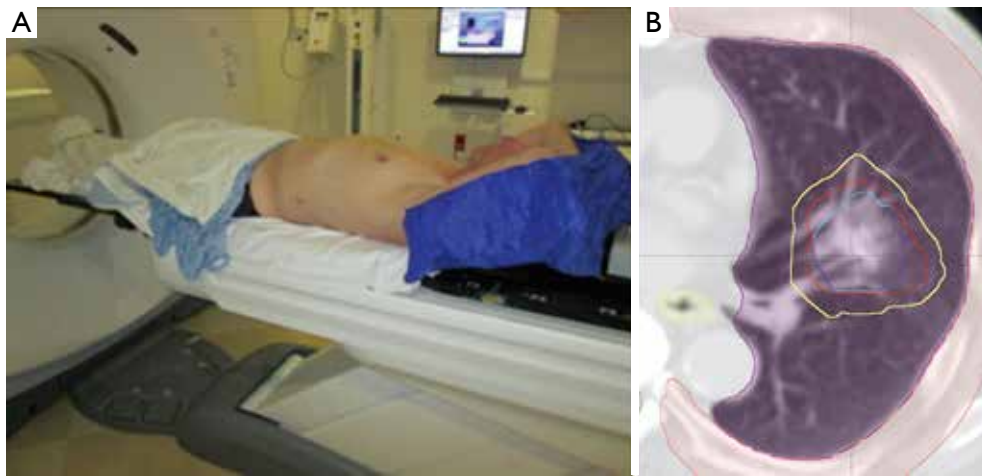


Figure 4 Typical patient setup for lung treatment (A) at Scripps Proton Therapy Center, and ITV contouring were derived for tumor with motion less than 1 cm.

Motion Management - SDX DIBH system

Patient voluntarily performs a breath hold in the target inspiration zone during CT imaging

SDX system

- Sensor
- Bacterial filter
- Mouthpiece
- Nose clip

SDX 2.1 module

SDX software

Video goggles*

*picture shown may vary from actual product

SDX trolley

Figure 5 Organ motion management with SDX Spirometric Motion Management System. This is used for tumor motion more than 1 cm.

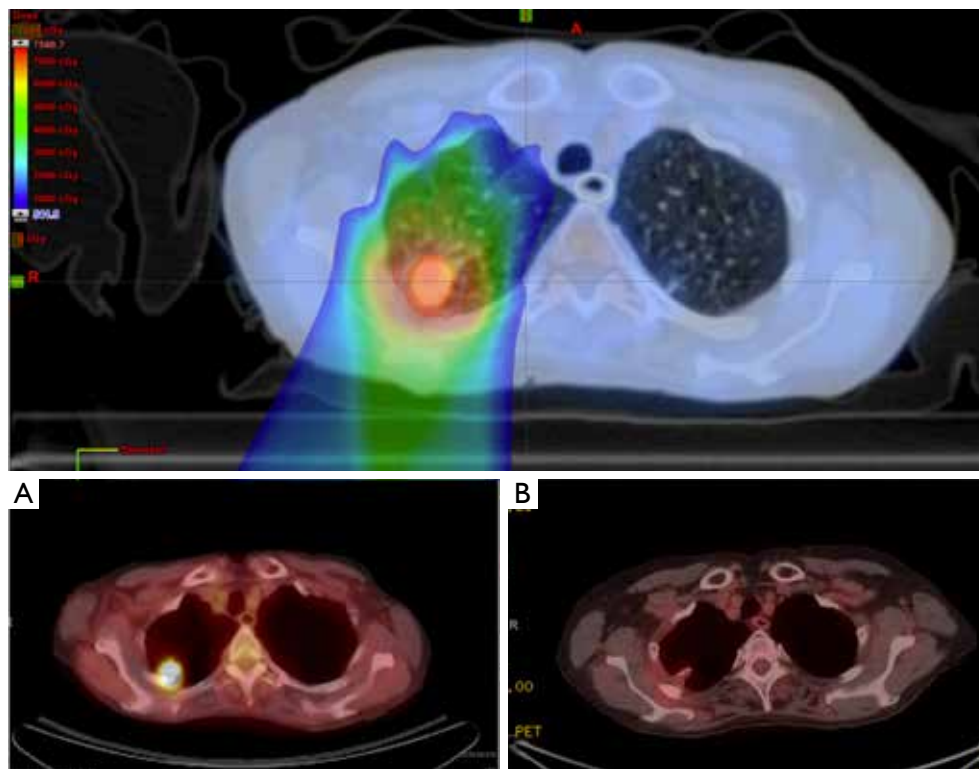


Figure 6 Organ motion management with SDX Spirometric Motion Management System is used for treatment of lung tumor with more than 1 cm motion for this T1 No Mo NSCLC. The PET/CT below showed the tumor before (A) and 8 months (B) after the treatment. NSCLC, non-small cell lung cancer; PET, positron emission tomography.

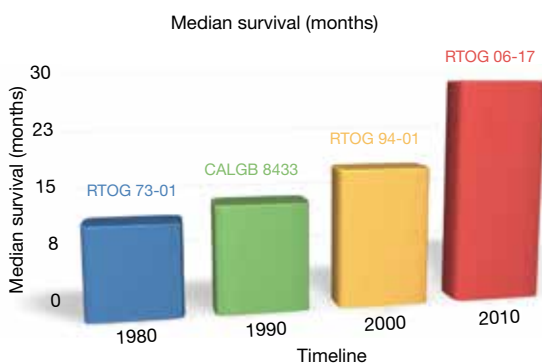


Figure 7 Improvement in median survival for stage II/III NSCLC over the last 40 years (32-36). NSCLC, non-small cell lung cancer.

NSCLC has improved from 12 months in the mid 1980 (RTOG 7301) to 29 months currently (RTOG 0617), as shown in *Figure 7*.

RTOG 9410 clinical trial demonstrated better median survival (17 months over 15 months) and lower local relapse rate (41% *vs.* 50%) of concurrent chemo-radiation over

sequential chemotherapy followed RT of 60 Gy. This gain is offset by higher rate of grade 3 or higher GI toxicity (23% *vs.* 4%). The grade 3 or higher lung toxicity is about 13-14% for these groups of patients. Elective nodal radiation was done in this study, and 3-D conformal photon radiation was used. RTOG 0617 compared dose escalation of 74 *vs.* 60 Gy, both are given concurrently with systemic therapy. The patients in the lower dose arm has better median survival of 28.7 *vs.* 20.3 months (36). This study does not use elective nodal irradiation and radiation was given by either 3-D conformal or IMRT technique with photon. Subsequent analysis of this study speculated that the lower survival in patients of higher dose group due to the cardiac toxicity, radiation pneumonitis and esophagitis, and possible geographic miss. There is a current prospective randomized study comparing proton versus photon IMRT (concurrent with platinum doublet chemotherapy) for stage II to IIIB NSCLC at MD Anderson and MGH. The maximum dose of 74 Gy in 2 Gy per fraction is prescribed if dose tolerance is achievable, if not, then dose is reduced by 2 Gy step

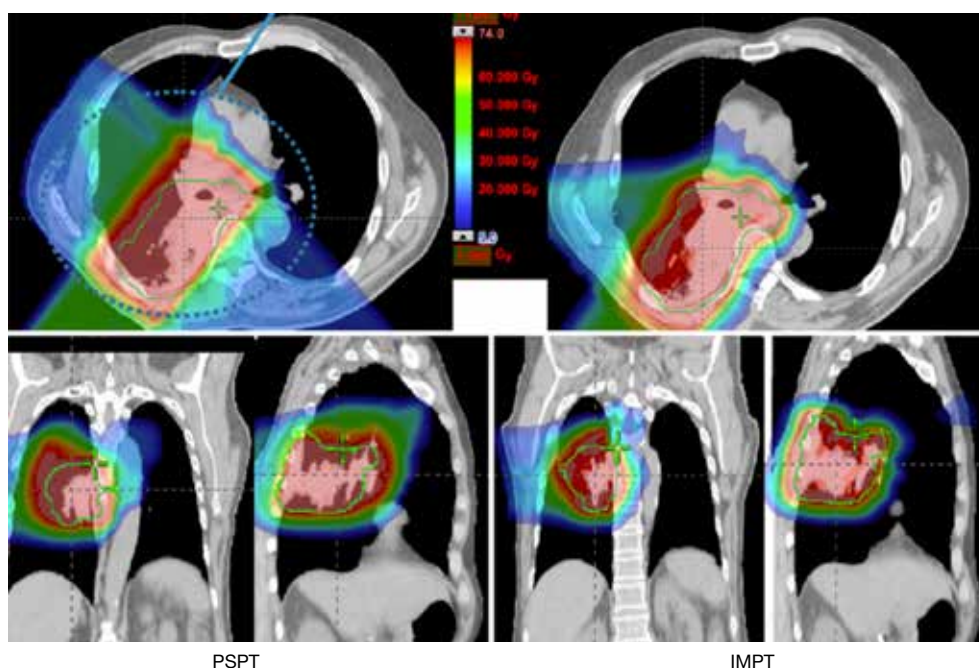


Figure 8 Comparing dose distribution of passive scatter proton therapy (left) and IMPT (right). IMPT has better dose conformity to target, normal organ sparing, and allow simultaneous boost. IMRT, intensity modulated radiation therapy.

until dose constraints to all OAR are met. This RTOG 1308 protocol has enrolled about 300 patients of total 560 patients at the time of this writeup, and the median heart dose is lower in the proton arm.

Chang *et al.* reported a phase II trial in which 44 patients were treated with proton therapy for a dose of 74 Cobalt Gray Equivalent (CGE) in 37 fractions with concurrent chemotherapy (carboplatin and paclitaxel) (37). In this study, the median OS was 29.4 months, PFS is 63% and OS is 86% at 1 year. Local failure was 9%, and no patient experienced grade 4 or 5 proton-related adverse events.

Sejpal *et al.* (38) compared the outcomes of PBT + chemotherapy (n=62), 3D-CRT + chemotherapy (n=74), and IMRT + chemotherapy (n=66) in patients with stage III NSCLC. The median total radiation dose was 63 Gy and 74 CGE respectively the photon and proton groups. The incidence of severe pneumonitis and esophagitis was lower in the proton group even with higher radiation dose. The median survival times were 17.7 months for the 3-D CRT group, 17.6 months for the IMRT group, and 24.4 months for the proton therapy group (P=0.1). It can be predicted that higher doses of PBT could be delivered to lung tumors with lower rates of esophagitis and pneumonitis, despite current concern regarding the apparent lack of benefit and potentially harmful of dose escalation in locally advanced

(stage III) NSCLC (36).

Grutters *et al.* (39) performed a meta-analysis of observational studies comparing photon, proton, and carbon-ion radiotherapy in the treatment of NSCLC, in which they concluded that proton beam radiotherapy did not offer a statistically significant improvement in OS when compared to photon-based stereotactic RT. However, both modalities were significantly better than conventional photon RT. Particle therapy may be more beneficial in stage III NSCLC, especially in reducing adverse events, and may spare lung volumes from receiving low-dose irradiation from exiting photon beams (39). Thus, proton therapy may offer an advantage by safely delivering higher doses within a short overall treatment time (hypofractionation) (40).

Majority of current proton therapy in the USA is done using passive scatter proton therapy. There are few centers exploring the use of pencil beam scanning. There are several modes of pencil beam scanning such as uniform scanning, spot scanning, raster scanning. A detailed descriptions is beyond the scope of this article. Pencil beam scanning allows the use of intensity modulated proton therapy (IMPT). IMPT is more subjective to organ motion; however, IMPT allows for better dose conformity and organ sparing. IMPT also allows simultaneous boost within the target volume. An example of dose distribution is shown in *Figure 8*.

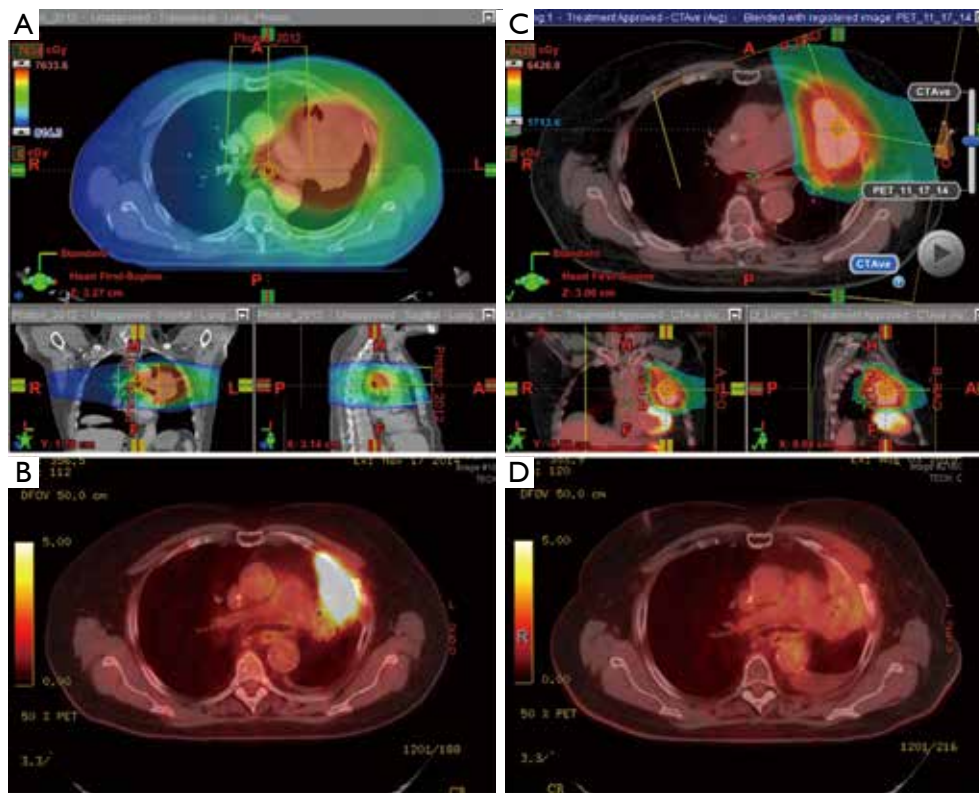


Figure 9 This 76 year old male with diagnosis of NSCLC (squamous cell carcinoma), who was treated concurrent chemotherapy and IMRT for 70 Gy in 35 fractions [panel (A)]. He then developed local recurrence about 2 years later [panel (B)], who then received salvage systemic chemotherapy for 6 months without change. He received salvage proton therapy using IMPT [panel (C)] for a dose of 66 Gy in 33 fractions with concurrent cisplatin. Patient tolerated the treatment well. He had a follow up with PET/CT 10 months later showing good response [panel (D)]. Patient is doing clinically well with no evidence of disease and no late toxicity. NSCLC, non-small cell lung cancer; PET, positron emission tomography; IMRT, intensity modulated radiation therapy.

Proton therapy for recurrent lung cancer

Patients, who have previous received RT and now with local recurrence, present a challenge to current treatment. They are often not a surgical candidate and systemic chemotherapy does not work well in this patient population. Re-irradiation with SBRT or proton therapy offers a new curative treatment modality with reasonable side effect profile. SBRT works well in patients with a small recurrence with lots of motions and not in central location (2 cm away from the main bronchus and trachea). SBRT is given with 5 or fewer fractions and chemotherapy is not given concurrently. For patient with larger tumor and/or nodal recurrence in area of less motion, proton therapy is a better option. Re-irradiation with proton therapy can be given as hypofractionated or standard fractionation regimen and can be given concurrently with systemic chemotherapy. The

larger and the more complex shape of the tumor, the better proton therapy is. The majority of these patients need sparing of the remaining healthy lung (even at low dose), heart, and esophagus. This is where proton excels. There are several phase I-II trials ongoing investigating role of proton therapy for this group of patients. *Figures 9,10* shows cases of re-treatment with IMPT for two patients with local recurrent NSCLC after previous radiation treatment.

Current clinical trials

At the time of this writing, there are 17 clinical trials that are investigating the use of proton therapy for lung cancer. Of the trials, 13 are open to patient accrual and 4 are closed. There is one pilot study, 13 phase I and/or II studies, one phase III study, and two medical physics studies. Ten of the trials are single institution, while the other seven are multi-

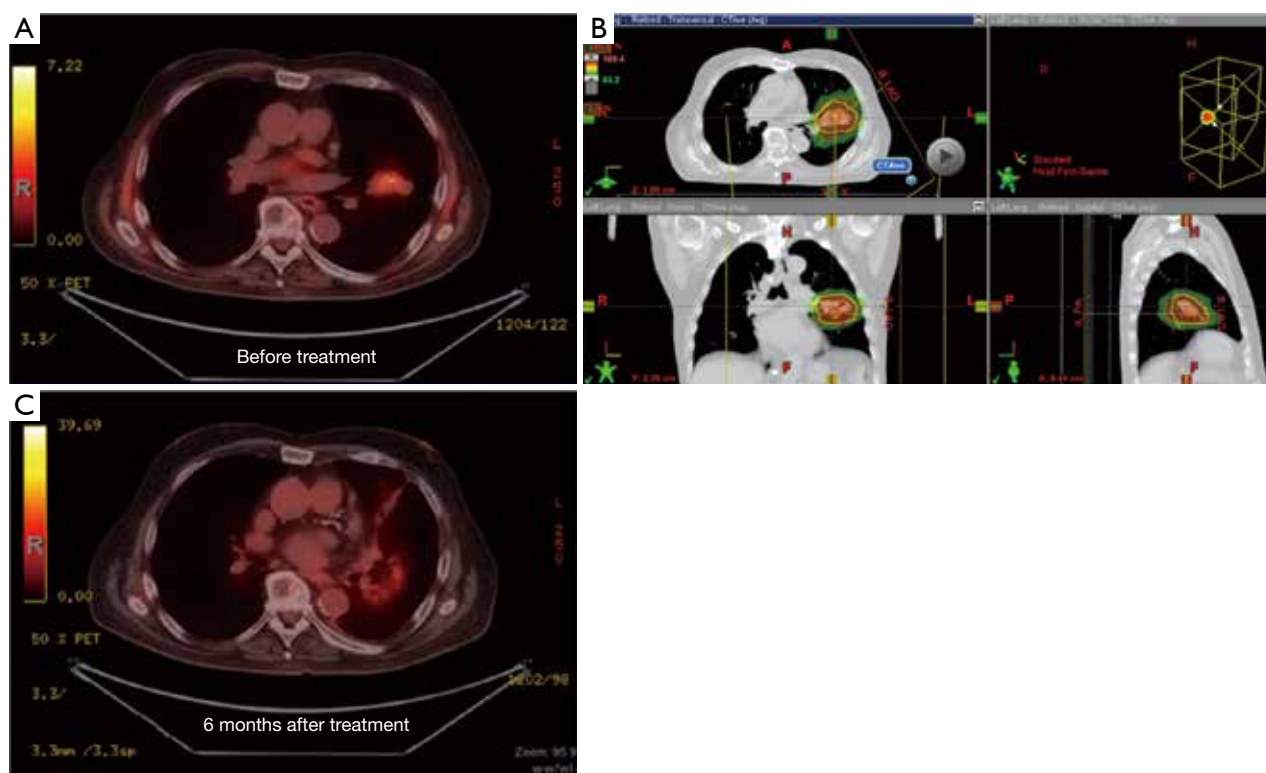


Figure 10 This 72 year old male with diagnosis of NSCLC (adenocarcinoma), who was treated with SBRT with CyberKnife for 54 Gy in 3 fractions. He then developed local recurrence about 3 years later [panel (A)]. He received salvage proton therapy using IMPT [panel (B)] for a dose of 63 Gy in 25 fractions to CTV and 80 Gy boost to the GTV with concurrent cisplatin. Patient tolerated the treatment well. He had a follow up with PET/CT 8 months later showing good response [panel (C)]. The area was re-biopsied and showing no evidence of malignancy. Patient is doing clinically well with no evidence of disease and no late toxicity. NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiation therapy; IMRT, intensity modulated radiation therapy.

institutional. Six of the trials involve combined modalities (i.e., concurrent chemotherapy). For more information about these clinical trials, please refer to the PTCOG website (www.PTCOG.ch) or clinicaltrials.gov. Areas under investigation with current clinical trials are:

- (I) Prospective randomized trial for stage II/III between photon and proton: RTOG-1308 is a phase 3 randomized study comparing proton versus IMRT, allowing the dose range of 60-74 Gy, similar to the RTOG 0617; however, with proton therapy, it is hoped that the reduction in critical structure dose (heart and lung) will improve survival. PCORI trial is being proposed by Dr. Brad Hoppe at University of Florida to compare proton versus photon for stage II/III;
- (II) Hypofractionation regimen for stage II/III. This is done to reduce the treatment cost of proton therapy and extending the experience from proton

therapy for early stage lung cancer. Dr. Brad Hoppe (University of Florida, USA) started a protocol with total of 60 Gy given 15, 17, 20, and 24 fraction regimens given concurrently with chemotherapy. Dr. Cliff Robinson (Washington University, USA) proposed 15 fraction regimen for total dose of 45, 48.75, 52.5, 56.25, and 60 Gy concurrently with chemotherapy;

- (III) SBRT boost to the primary tumor after treating the mediastinal nodes with proton therapy. Dr. Kristin Higgins (Emory University, USA) proposed 44 Gy given in 22 fractionations, followed by boost to primary tumor with SBRT with following regimens, 18 Gy in 2 fractions, 20 Gy in 2 fractions, 30 Gy in 5 fractions, 30 Gy in 5 fractions, 35 Gy in 5 fractions and 40 Gy in 5 fractions;
- (IV) Proton therapy for post-op treatment for patients with N2 disease. Drs. Cliff Robinson (Washington

University, USA) and Charles Simone (University of Pennsylvania) proposed a randomized trial of photon versus proton for post-op radiation of patients with stage IIIA (pN2) for dose of 50.4 to 54 Gy;

- (V) Re-irradiation protocols for patients who received previous radiation to the lung or nearby area. There are several institutions investigating this area.

Conclusions

The unique properties of proton therapy allow the sparing of normal structures around the target tumors, which could be beneficial for lung cancer patients with tumors near critical structures, limited pulmonary reserve, or with larger tumors (3). Proton therapy can lower the risk of treatment side effects and provide a valuable tool for dose escalation or re-irradiation. Implementation of proton therapy is currently hindered by the cost of the technology and limited approval from healthcare payers. Per treatment fraction, proton therapy is more expensive than standard photon therapy. However, if one factors into the cost of treatment excess side effects and sequential mortality and also the new hypofractionation schemes, proton therapy can be established to be cost-effective for the management of selected cases of lung cancer (41). The current argumentation tends to overlook the existing evidence on clinical- and cost-effectiveness data. Patients deserve the best technology available, on the medical and ethical basis of the best available evidence. Therefore, when analyzing new and emerging technologies, all risks of treatment-related side effects and complications, as well as all possible clinical improvements, need to be taken under consideration (42,43).

On another front, with more vendors available, there are more competitions to have the equipments less expensive, more reliable with more features. Technology and its implementation continue to improve on a daily basis. Pencil beam scanning including IMPT may produce better clinical results than scattered PBT (11). More research is needed to successfully optimize proton delivery treatments. Improvements are needed to optimize the motion management, volumetric image guidance, and adaptive therapy. More research is needed to create plans that are more robust in the face of uncertainty, especially for the new pencil beam scanning systems. Additional prospective trials for lung cancer are needed to clarify the category of patients that will benefit the most from proton therapy. Findings of increased quality of life, LC, and survival will hopefully lead

to greater cost-effectiveness in the future.

Acknowledgments

None.

Footnote

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

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Cite this article as: Giap H, Roda D, Giap F. Can proton beam therapy be clinically relevant for the management of lung cancer? *Transl Cancer Res* 2015;4(4):E3-E15. doi: 10.3978/j.issn.2218-676X.2015.08.15

Chemoradiotherapy for stage III non-small cell lung cancer: have we reached the limit?

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Lung cancer is the leading cause of cancer-related mortality in men and the second leading cause in women. Approximately 85% of lung cancer patients have non-small cell lung cancer (NSCLC), and most present with advanced stage at diagnosis. The current treatment for such patients is chemoradiation (CRT) provided concurrently preferably or sequentially with chemotherapy, using conventionally fractionated radiation doses in the range of 60 to 66 Gy in 30 to 33 fractions. An individual patient data based meta-analysis has shown that in good performance status (PS), concomitant CRT was associated to improved survival by 4.5% compared to sequential combination (5-year survival rate of 15.1% and 10.6% respectively). In the recent years, improvement of modern technique of radiotherapy (RT) and new chemotherapy drugs may be favorable for the patients. Furthermore, the positron emission tomography-computed tomography (PET-CT) contributes to improved delineation of RT especially in terms of nodal involvement. Improving outcomes for patients with stage III disease remains a challenge, this review will address the questions that are considered fundamental to improving outcome in patients with stage III NSCLC.

Keywords: Lung cancer; non-small cell lung cancer (NSCLC); locally advanced inoperable; combined chemoradiotherapy (combined cRT)

Submitted May 15, 2015. Accepted for publication Oct 15, 2015.

doi: 10.3978/j.issn.2304-3865.2015.11.04

View this article at: <http://dx.doi.org/10.3978/j.issn.2304-3865.2015.11.04>

Worldwide, lung cancer is the leading cause of cancer deaths in men and the second leading cause of cancer deaths in women. Based on the GLOBOCAN 2012 estimates, about 1.9 million new lung cancer cases and 1.6 million deaths expected to occur (1). Approximately 85% of lung cancers are non-small cell lung cancers (NSCLC) and only 25-30% of these are eventually suitable for surgical resection with a curative intent (2). At present, the 5-year survival of resected patients ranges between 75% for stage IA and 25% for stage IIIA (2). The current treatment strategy for NSCLC depends on clinical staging. Surgical resection is generally considered the treatment of choice in operable patients with stage I and II disease (3,4). Conversely the role of surgery for stage III NSCLC patients continues to be debated (5-7).

Treatment decisions concerning patients with stage III disease, have to be taken upfront; ideally within a multidisciplinary thoracic tumour board to decide the optimal strategy taking into consideration the anatomical characteristics of the tumour as well as performance status (PS) and ability to undergo surgery, high-dose radiotherapy (RT) and chemotherapy (8,9). The first decision is usually to decide whether the patient is potentially operable, and surgery will be discussed for most stage IIIA patients and some selected stage IIIB patients, whereas most stage IIIB patients will be eligible for combined chemoradiation (CRT) (9). Thus most patients with inoperable stage III disease

will be candidates for combined modality chemotherapy and RT. While concomitant administration improves survival compared to sequential combination as shown in several meta-analyses, there is a higher rate of acute toxicities, especially esophageal toxicities (9-13). While the randomized trials have provided evidence in favor of concurrent chemoradiotherapy (cCRT), there is place for improvement for future research and protocols to optimize chemoradiotherapy. The 5-year survival with concomitant platin based CRT is 15.1% in the meta-analysis and 16% in the largest randomized trial included, the Radiation Therapy Oncology Group (RTOG 9410) with median survival rate of 17 months whereas the 5-year survival in the sequential CRT arm is 10.6% in the meta-analysis and 10% in the RTOG trial (11,14). It should be outlined that the patients included in the trials included in the meta-analysis were treated between 1988 and 2003, before the positron emission tomography-computed tomography (PET-CT) era. It is superior to CT to rule out detectable extrathoracic extracranial metastasis and to assess potential mediastinal lymph node involvement. More recently, a randomized trial (RTOG 0617) evaluating both dose escalation from 60 to 74 Gy as well as the addition of cetuximab to concomitant CRT was published. The median survival in the control arm was 28.7 months for patients with stage III disease treated with cCRT at the dose of 60 Gy (15). It should be outlined that 90% of patients were selected with PET-CT,

and improved survival compared to previous studies is partly due to better selection. Part of the improvement may also be explained by more modern technique of RT and more conformal RT as indirectly shown in retrospective studies (16,17).

Improving outcomes for patients with stage III disease remains a challenge, this review will address the questions that are considered fundamental to improving outcome in patients with stage III NSCLC.

Radiotherapy (RT)

Changes in radiotherapy (RT) technology

Historically, thoracic RT planning has been complicated by difficult target delineation, unquantifiable tumor motion, all issues that may have led to geographic miss using conventional RT. There have been major changes in the past 15 years due also to the systematic implementation of PET-CT into radiation treatment planning (18,19). PET CT contributes to improved delineation especially in terms of nodal involvement, as well as difficult situations such as tumor with atelectasis. It should be performed ideally within 4 weeks before the start of treatment. We have no randomized data to support that contemporary conformal RT with the implementation of PET-CT increases local control and potentially survival. There are however retrospective studies that seemed to show a beneficial effect of the use of more modern RT techniques in stage III NSCLC patients (16,17).

Compared with 3D-CRT, intensity-modulated radiation therapy (IMRT) enables even tighter sculpting of high-dose regions around the tumor volume, creates steep dose gradients and thus reduces radiation dose to surrounding normal tissues, ultimately facilitating dose-escalation (20). The University of Texas M.D. Anderson Cancer Center investigated the rate of high-grade treatment-related pneumonitis in patients with advanced NSCLC treated with concurrent chemotherapy and IMRT. Toxicity rates were compared with a similar cohort of patients treated with 3D-CRT (median radiation dose 63 Gy for both treatment modalities). The levels of grade ≥ 3 radiation pneumonitis at 12 months according to RTOG toxicity scoring were significantly ($P=0.002$) lower for IMRT than for 3D-CRT, being 8% [95% confidence interval (CI), 4-19%] and 32% (95% CI, 26-40%), respectively (21). This initial evaluation is consistent with the conclusion of a subsequent study, including more patients and with

longer follow-up times (17). Out of 496 NSCLC patients, 318 were treated with CT/3D-CRT and 91 with 4DCT/IMRT. The hazard ratio (HR) for 4DCT/IMRT was 0.33 (95% CI, 0.13-0.82; $P=0.017$) for grade ≥ 3 radiation pneumonitis, indicating lower toxicity rates were associated with 4DCT/IMRT. These findings were confirmed by other studies (22,23). Furthermore, IMRT reduces radiation doses to the esophagus, heart and spinal cord (23,24).

The following solutions could be considered to allow using IMRT to both primary and lymph node areas. A reduction in the planning target volume (PTV) margin may allow for dose escalation for more patients using IMRT. We could use 4DCT for getting the data on systematic and random movements of the proximal bronchial tree and great vessels, and generate the most appropriate margin (25); use of daily online cone-beam CT to decrease CTV to PTV margins (26).

Changes in radiation dose

Dose-escalation studies of three-dimensional conformal RT seem to show that in a 63-103 Gy range, a higher radiation dose increased local control of the tumor and OS (27). However other studies did not result in better outcome. The clinical practice of stereotactic body irradiation for NSCLC confirms this hypothesis that higher doses of RT may result in better outcome: the survival of patients who received RT at a BED ≥ 100 Gy was significantly better than those who received a BED of less than 100 Gy (28).

Although phase I/II dose-escalation studies of conventional fractionated RT with concurrent chemotherapy reported encouraging survival outcomes obtained with the high dose of 74 Gy (29,30), the results of the subsequent phase III randomized did not confirm these results (15). In the latter study, 166 patients were randomly assigned to receive carboplatin-paclitaxel based chemoradiotherapy with 60 Gy considered as the standard RT dose, 121 to high-dose chemoradiotherapy (same regimen with RT at the dose of 74 Gy), 147 to standard-dose chemoradiotherapy and cetuximab, and 110 to high-dose chemoradiotherapy and cetuximab. Median follow-up for the RT comparison was 22.9 months (IQR, 27.5-33.3). Median overall survival was 28.7 months (95% CI, 24.1-36.9) for patients who received standard-dose RT and 20.3 months (17.7-25.0) for those who received high-dose RT (HR 1.38, 95% CI, 1.09-1.76; $P=0.004$). Both the radiation-dose and cetuximab results crossed protocol specified futility boundaries. The authors recorded no statistical differences

in grade 3 or worse toxic effects between RT groups. There were no differences in severe pulmonary events between treatment groups. Severe esophagitis was more common in patients who received high-dose chemoradiotherapy than in those who received standard-dose treatment [43 (21%) of 207 patients *vs.* 16 (7%) of 217 patients; $P < 0.0001$] (19). The authors have concluded that dose escalation for all patients at the dose of 74 Gy could be harmful. There are ongoing studies exploring a more selective dose escalation.

NSCLC is a rapidly proliferating cancer, and accelerated repopulation occurs during RT. Thus another area of possible RT intensification is altered fractionation. An individual data based meta-analysis showed that modified fractionation (hyperfractionated and/or accelerated RT) improved survival as compared with conventional schedules resulting in an absolute benefit of 2.5% (8.3% to 10.8%) at 5 years ($P = 0.009$). In a RTOG retrospective study evaluating treatment duration in several CTRT prospective studies, overall treatment time exceeding by over 5 days the theoretical duration, was associated with a 2% increase in the risk of death for each day of prolongation in therapy (31). Prolonged overall treatment time may be one of the reasons why high-dose RT in the RTOG 0617 study failed to produce any survival benefit as treatment time was 7.4 weeks long (32).

Changes in radiation fractionation

Several studies have shown that higher biologically effective doses (BEDs) of RT in cancer treatments could improve local control and survival (32-34). An analysis demonstrated a moderate linear relationship between lesional BED and overall survival: for every 1 Gy increase in BED, there was an absolute overall survival benefit ranging from 0.36% to 0.7% (35). Because dose escalation with conventional fractionation requires a significant increase in treatment time, two methods to improve BED that maintain or reduce treatment time have been explored: hyperfractionation and hypofractionation.

Accelerated hypofractionated irradiation (AHRT) is infrequently used for the treatment of locally advanced NSCLC. Several studies have explored AHRT combined with chemotherapy with some interesting results (36-44). However hypofractionation particularly in the context of concurrent CRT may cause severe adverse effects on the lung and soft tissues of chest wall, so that it cannot be recommended outside a clinical trial (45). A randomised phase II trial comparing sequential versus concurrent

chemotherapy and radical hypofractionated RT at the dose of 55 Gy in 20 fractions of 2.75 was recently published and showed similar survival rates at 2 years of 50% and 46%. Hypofractionated dose-escalated RT with IMRT at doses from 57 to 85.5 Gy in 25 daily fractions over 5 weeks was explored in a phase I study. The maximum tolerated dose was 63.5 Gy; late toxicity was dominated by late radiation toxicity involving central and perihilar structures (45). It should be outlined that no concomitant chemotherapy was administered in this study.

Recently, high-precision RT such as intensity-modulated RT, image-guided RT, treatment gating, have made this approach more feasible. Compared to prior RT approaches, IMRT can significantly lower the doses of radiation to normal tissues, allowing for the administration of larger doses per fraction on tumors. The hypofractionated regimen of 55 Gy in 20 fractions is one of the most common fractionation schedules in the United Kingdom (44).

In the UK, a very dose intense approach, a continuous hyperfractionated accelerated radiotherapy (CHART) was evaluated in NSCLC (32). Patients were randomly assigned to receive the dose of 54 Gy provided in 12 consecutive days (including weekends) with 1.5 Gy administered 3 times per day, or 60 Gy in conventional fractionation. This trial showed a significant benefit in favor of the investigational arm as there was a 24% reduction in the relative risk of death, a 9% absolute improvement in 2-year survival. However these results were not confirmed in the CHARTWEL-trial whether patients were randomly assigned to the CHART week-end less regimen (60 Gy/40 fractions/2.5 weeks) or to control arm (66 Gy/33 fractions/6.5 weeks) (46). Overall, outcome was not different in both arms with 2- and 5 year-survival respectively 31% and 11% in the CHARTWELL arm and 32% and 7% in the control arm ($P = 0.43$). There was a trend for higher efficacy in higher stages and after induction chemotherapy. Both trials were included in the meta-analysis exploring the role of altered fractionation in lung cancer; it demonstrated a 2.5% absolute overall survival benefit at 5 years over conventional fractionation (33).

However, such accelerated treatment may induce more acute toxicity (especially esophagitis) But a further study of cost effectiveness of altered fractionation schedules compared to standard regimen seems to show that accelerated RT may be more efficient and should be recommended as standard RT for the curative treatment of unresected NSCLC patients not receiving concurrent chemo-radiotherapy (33,47).

One could expect less toxicity with newer RT techniques such as IMRT. In the study of Yom *et al.* (21), where

4D IMRT enabled less high grade pneumonitis than it was observed with 3DRT (8% *vs.* 32% at 12 months, respectively). More clinical research is needed in this field to provide deeper insight into the problem of high-grade toxicity of hyperfractionated RT with concurrent CT. In the meta analysis exploring for predictive factors of pneumonitis, after combined CRT using either 3-D conformal RT or IMRT, older age, use of carboplatin and paclitaxel concomitant chemotherapy as well as dosimetric parameters were predictive of symptomatic pneumonitis (48). Based on this study, the rate of pneumonitis (\geq grade 2) was 29.8%; only 1.9% was fatal. Daily doses over 2 Gy (7% if >2 Gy *vs.* 1.5% if ≤ 2 Gy; $P=0.01$), V20 (OR, 1.09 per 1% increase, $P=0.044$), and tumor location (1% for upper lobe, 0% for middle lobe, and 5% for lower lobe, $P=0.007$) were found to be associated with fatal pneumonitis in this meta-analysis. The same group performed another individual data based meta-analysis to explore to determine factors predictive of clinically significant radiation esophagitis. Based on the data of over 1,000 patients, the risk of grade 2, grade 3 and grade 4 esophagitis was respectively 32.2%, 17.1%, and 0.9%. The value of V60 was the best predictor for radiation esophagitis (49).

Chemotherapy

Changes of chemotherapy timing

cCTRT is widely used throughout the world as standard of care for inoperable stage III NSCLC patients with good PS and limited co-morbidities (6,9,11,12,50-57). Concurrent CRT may be offered to selected elderly patients, but it should be outlined that there is a higher risk for toxicity reported in the elderly population (57). In a large meta-analysis ($N=1,205$) of chemotherapy in locally advanced NSCLC, concomitant chemoradiotherapy, as compared with sequential chemoradiotherapy, produced significant improvements in overall survival (HR, 0.84; 95% CI, 0.74-0.95), 3-year survival (absolute benefit of 5.7%), and 5-year survival (absolute benefit of 4.5%) (11), while the advances have been made in improving survival from stage III NSCLC by optimizing local control, latest evidence suggests that cc CTTRT does not reduce the risk of distant relapse. But randomized trials having evaluated induction or consolidation chemotherapy added to concomitant CRT do not seem to improve survival (9,58-60). The phase III trial which evaluated consolidation CT after treatment with cCTTRT compared consolidation docetaxel (75 mg/m²

every 21 days) for three cycles *vs.* observation (58). The trial was terminated early after planned interim analysis on the basis of futility. No significant difference in median survival between the docetaxel and observation arms was observed (21.2 *vs.* 23.2 months, $P=0.883$). There were higher rates of grade 3-5 pneumonitis in the docetaxel arm compared to the observation arm (9.6% *vs.* 1.4%, $P<0.001$) and a subsequent analysis of the data confirmed that treatment with consolidation docetaxel was a predictive factor for radiation pneumonitis following cCTTRT (61). A recent pooled analysis of 41 phase II/III trials has confirmed that there is no evidence to suggest that consolidation chemotherapy after cCTTRT improves survival for stage patients with III NSCLC (60).

In general, the highest incidence of NSCLC is observed in patients older than 65 years. As a consequence, a considerable percentage of patients with newly diagnosed NSCLC are frail and unfit for concurrent RCT treatments. More than half of patients are theoretically not eligible for concurrent RCT in a population-based study (61). Intensification of both RT and concurrent chemotherapy may result also into excessive toxicity or incomplete treatment (57,61). Less toxic alternatives are needed for these patients.

Changes in the chemotherapy drugs

The current standard for locally advanced NSCLC is conformal RT administered at the dose of 60-66 Gy combined with concurrent platinum-based regimen (9,11,49,50,52,53). Etoposide-cisplatin, cisplatin-vinorelbine as well as paclitaxel-carboplatin are commonly used with concurrent radiation therapy in locally advanced NSCLC.

The broadest evidence concerning this issue comes from trials that have included cisplatin based doublets, particularly, cisplatin and etoposide or cisplatin and vinorelbine (9). Despite this accepted evidence, there has been a strong trend in North America and even in parts of Europe to prefer outpatient administration of weekly low-dose carboplatin and paclitaxel combination schedules that are simultaneously administered with outpatient RT, on the basis of the assumption that this is more convenient and possibly just as effective as cisplatin-based doublets (9). It should be outlined that the concomitant administration of carboplatin-taxol as well as docetaxel administered concomitantly or as consolidation treatment seems to increase the rate of pneumonitis (48,54,55).

Santana-Davila *et al.* (62) tried to evaluate the optimal CRT regimen, in a large retrospective study from the Veterans

Health Administration (VHA) database of 1,842 patients treated over a 10-year period (2001 to 2011). They compared patient groups receiving either cisplatin and etoposide, or a combination of carboplatin and paclitaxel, administered concurrently with curative doses of radiation. The aim of their study was to compare the two chemotherapy protocols with respect to the survival outcome. They concluded that carboplatin and paclitaxel, when administered concurrently with RT, resulted in survival outcomes that were comparable to cisplatin and etoposide in a comparable clinical setting. However one should always be cautious with such a posteriori comparisons. This cannot be considered as robust evidence in favour of one treatment modality. It should be outlined that carboplatin may also not be as effective as cisplatin against micro metastases in lung cancer, as we have learned a meta-analysis on metastatic NSCLC which showed that cisplatin-based chemotherapy was slightly superior to carboplatin-based chemotherapy in terms of response rate and, in certain subgroups, in prolonging survival without being associated with an increase in severe toxic effects (63). A subsequent meta-analysis comparing cisplatin doublets to carboplatin doublets combined to third generation drugs in metastatic NSCLC did not show any difference in survival but a better response rate with cisplatin doublets (64). It should be recalled that all trials that have evaluated carboplatin alone with RT were negative (65). On the basis of the published evidence from the meta-analysis that used individual patient data (48), it was found that carboplatin/paclitaxel might be even more toxic than the cisplatin/etoposide combination with respect to the development of pneumonitis. Pulmonary toxicity remains a sensitive issue for such a curative treatment. It also has clinically relevant implications for quality of life and well-being of patients, based on the development of late effects from chemoradiotherapy (48).

A number of other drugs have been investigated for combined modality treatment and the development of newer chemotherapeutic agents with activity in NSCLC provides the opportunity to explore novel approaches in the treatment of stage III disease, as pemetrexed which has become one of the major drugs in metastatic adenocarcinoma. According to a current review of the literature of phase I and phase II studies (66), it seems pemetrexed can be administered safely at full systemic doses with cisplatin concomitantly with radical doses of thoracic RT. Of the six phase II trials with mature data available, median overall survival ranged from

18.7 to 34 months. However, we should wait for the results of the phase III trial PROCLAIM which has not been published yet. The trial has been presented at the ASCO meeting 2015 (67). It shows that pemetrexed and cisplatin may be safely administered, but is not superior in terms of efficacy to cisplatin and etoposide in the concurrent setting. Median survival, 2- and 3-year survival rate was respectively 26.8 months, 52% and 40% in the pemetrexed-cisplatin based CTRT arm and 25 months, 52% and 37% in the control arm combining RT at the dose of 66 Gy with etoposide and cisplatin.

In conclusion, it is clear that cCTR is the current standard of care for inoperable stage III NSCLC patients with good PS and minimal co-morbidities. However, a survival plateau has been reached, with disappointing results from dose escalation studies using conventional fractionation and studies investigating the addition of systemic doses of chemotherapy delivered before or after concurrent CRT. Further improvement such as IMRT/IGRT utilized for more selective dose escalation and to reduce dose to critical structures will be determined by better local control and by reducing the risk of distant recurrence. The benefits of newer chemotherapeutic agents will reduce both the risk of local and distant relapse. Collaborative efforts are now needed to these advances for optimal treatment and improved outcomes of locally advanced NSCLC.

Acknowledgements

None.

Footnote

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

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Cite this article as: Xu P, Le Pechoux C. Chemoradiotherapy for stage III non-small cell lung cancer: have we reached the limit? *Chin Clin Oncol* 2015;4(4):45. doi: 10.3978/j.issn.2304-3865.2015.11.04

Overcoming toxicity-challenges in chemoradiation for non-small cell lung cancer

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Abstract: Concurrent chemoradiation (CCRT) is the treatment of choice for locally advanced non-small cell lung cancer (NSCLC) with a modest survival benefit over sequential chemoradiation or radiotherapy (SCRT) alone. However, this benefit is at the cost of increasing acute toxicity such as esophagitis. Previous analysis revealed several predictive parameters in dose-volume and patient characteristics which helped us to identify those patients at risk for severe esophagus toxicity. As a result, supportive care interventions including individualized patient information, dietary guidance, adequate medication, hydration and tube-feeding could be initiated. This paper discusses the challenges in overcoming chemoradiation induced acute esophageal toxicity (AET).

Keywords: Chemoradiation; supportive care; toxicity; management

Submitted Jan 27, 2016. Accepted for publication Mar 09, 2016.

doi: 10.21037/tlcr.2016.05.03

View this article at: <http://dx.doi.org/10.21037/tlcr.2016.05.03>

Introduction

This paper will discuss the challenges in preventing and managing chemoradiation induced acute esophageal toxicity (AET). Following a clinical summary of AET, the current guidelines from the Netherlands Cancer Institute will be discussed including a case study.

Concurrent chemoradiation (CCRT) is the treatment of choice for locally advanced non-small cell lung cancer (NSCLC). The increase in survival for concurrent versus sequential chemoradiation (SCRT) (+5.7% at 3 years) or radiotherapy (RT) alone (+7% at 3 years) is mainly due to an improvement in local control of the disease (1). Several radio sensitizing agents are in use (2) and daily low dose cisplatin has shown to be an effective treatment regimen (3,4). Because of a milder hematological toxicity profile, more patients are able to benefit from this treatment compared to regimen using high dose chemotherapy (5-9). However, recent analysis revealed that 35% of the patients suffered from severe acute toxicity, including anorexia, nausea and vomiting, esophagitis and dehydration. Mediastinal tumor location and/or lymph nodes are common in locally advanced NSCLC patients, resulting in

the involvement of the esophagus in the radiation field. Due to the sensitizing effect of cisplatin, the incidence of AET is higher in CCRT compared to SCRT or RT only (10,11). Mucosal inflammation (12) and edema of the esophagus causes functional impairment, and is clinically described as a blocking sensation or pain when swallowing. Severe AET usually leads to weight loss, dehydration and malnutrition, requiring intravenous hydration, tube feeding or even hospitalization (13). As it is believed that the completion of CCRT optimizes the beneficial sensitizing effect, we took efforts to increase the management of this toxicity caused by CCRT. Although it is recognized that a range of toxicities needs to be addressed, AET is one of the most burdensome which can lead to clinical impairment and a severe reduction in quality of life.

In the last few years, several pro-and retrospective analyses in the Netherlands Cancer Institute led to increased knowledge on incidence, timelines and RT dose-effect relation of acute esophagus toxicity. This knowledge was used for initiating proactive supportive care management, patient education and the recalculation of RT restraints (13-15).

Table 1 Esophagitis: a disorder characterized by inflammation of the esophageal wall

Grade 1
Symptomatic and altered eating/swallowing
Grade 2
Symptomatic and altered eating/swallowing
Grade 3
Severely altered eating/swallowing; tube feeding or total parenteral nutrition or hospitalization indicated
Grade 4
Life-threatening consequences urgent intervention indicated

Patients and treatment

Aproximally 90 patients with cytological or histological proven locally advanced NSCLC are treated with CCRT in the Netherlands Cancer institute every year. Treatment consists of cisplatin 6 mg/m² as a 10 mL bolus injection, 1–2 hours prior to RT, for a total of 24 administrations over a period of 32 days. The standard RT consists of 24 fractions of 2.75 Gy, resulting in a total dose of 66 Gy to the primary tumor and involved lymph nodes. In case of large tumors or re-irradiation, where the mean lung dose exceeds 20 Gy, an alternative RT fractionation scheme is applied without changing the administration of cisplatin. All patients are treated with 7-field intensity modulated radiotherapy (IMRT) (3).

In case of severe comorbidities, a too large tumor volume, high age and/or a decreased performance status, patients are treated with SCRT or RT only.

Acute esophagus toxicity

Acute toxicity is defined as toxicity occurring with 3 months after treatment. Recent analysis showed that AET grade 2 occurred in 37% of the patients and grade 3 in 20%. The median onset was day 15 with a maximum grade at day 30 and of the grade 3 patients 48% recovered to grade 0 within 3 months. The median duration was 43 days for grade 1, 50 days for grade 2 and >80 days for grade 3. For grade 2 analgesics and dietary supplements are required, for grade 3 tube feeding and/or hospitalization (*Table 1*) (13).

Acute radiation esophagitis is primarily due to effects on the basal epithelial layer of the esophageal mucosa.

The normal esophageal mucosa undergoes continuous cell turnover and renewal. RT causes a thinning of the mucosa and as a result progresses the peeling.

A prospective study from the Netherlands Cancer Institute of 139 patients with inoperable NSCLC treated with IMRT and concurrent chemotherapy aimed to analyze predictive parameters for AET with the dose effect relationship between AET and dose volume parameters investigated (14). Before the introduction of IMRT, 3D-conformal radiotherapy (3DCRT) was the standard technique used for radical treatment. The treatment planning esophagus constraint at that time was the length of the esophagus ≤ 12 cm. Because this constraint was found insufficient in patients treated with 3DCRT and concurrent chemotherapy, a derived V35 (relative volume of the esophagus receiving more than 35 Gy) model was scaled (14). However, with IMRT dose-distributions and dose-volume-parameters for the esophagus having changed, it was concluded that V35 was no longer sufficient as well. It was revealed that in IMRT the relative volume of the esophagus treated with 50 Gy (V50) was a more predictive parameter for AET (14). In addition to these findings patient and treatment characteristics were analyzed in relation to AET, including the V50 model. Univariate and multivariate analyses were performed to correlate clinical, tumor, dosimetric and chemotherapy dose variables to AET grade ≥ 2 and grade 3. V50 (oes), ethnic background, and the number of cisplatin administrations were significantly correlated with grade 3 AET (13). As CCRT is associated with a favorable overall survival of 35% at 3 years, a certain risk on grade 3 AET is deemed acceptable since the toxicity is often temporary and manageable. However, in our study, grade 3 patients had a low recovery rate (48%) within 3 months and a long median duration (>80 days). We concluded that 52% of grade 3 patients are subjective to a risk of developing late esophagus toxicity, which in the severe cases (e.g., stenosis and fistula) could deteriorate the long-term quality of life, or even compromise survival (15).

Management of acute esophagus toxicity

In order to identify and categorize patients with AET by its severity the CTC classification is used in clinical practice (*Table 1*) as it helps to communicate and initiate clinical guidelines.

We present below the clinical guidelines that have been developed and introduced in the Netherlands Cancer Centre.

*Weight loss and nutritional guidelines***Before treatment**

In case of 5% weight loss in 1 month or $\geq 10\%$ in the last 6 months before treatment nutritional food supplements are administered.

During treatment

When the patient loses 5% of body weight loss in one month or 2 kg per week, tube feeding is started. This is also the case when there are clinical or biochemical signs of dehydration with an oral intake of maximum 1,000 mL/day.

After treatment

As per during treatment.

Analgesia

In case of grade 2 AET, paracetamol, sucralfate and proton pump inhibitors are administered, eventually with codeine or tramadol with additional laxation. In case of grade 3, durogesic transdermal and Abstral sublingual or instanyl nasal spray are added to paracetamol suppository. Also, tube feeding is indicated. In case of uncontrollable pain, the patient is admitted in the hospital for intravenous analgesics. In case of a superimposed candida infection, treatment with fluconazole is indicated.

Dehydration

Approximately 19% of the patients were not able to finish the complete 24 administrations of cisplatin because of a significant increase of the serum creatinine (7). This was mainly due to the inability of drinking enough fluids because of esophageal pain. In 2011 we started to prehydrate patients before the cisplatin bolus injection. The prehydration consisted of 1 L of natriumchloride (NaCl) 0.9% intravenously administered in one hour. In case of a history of cardiac failure or the occurrence of the syndrome of inappropriate anti-diuretic hormone secretion (SIADH), patients were given 500 mL of NaCl 0.9%. In the prehydrated group, only 2% discontinued treatment ($P=0.001$) (16). Surprisingly, the incidence of AET grade ≥ 2 decreased following prehydration: 62% *vs.* 34% ($P<0.001$) for the non-prehydrated and the prehydrated group, respectively (7).

V50

In case $\geq 30\%$ of the esophagus receives 50 Gy, there is a significant risk of AET grade 3. This information is useful for initiating proactive interventions such as the insertion of a percutaneous endoscopic gastrostomy and the administration of pantoprazole.

Case study

Mrs X is a 52-year-old patient, married, with two teenage children. She has a history of atrial fibrillation and is a former smoker with 40 pack years. In 2014 she developed a cT2N2M0 (Stage IIIa) adeno carcinoma of the right lung with positive lymph nodes in Naruke 7 for which CCRT was indicated. In the 3rd week of treatment swallowing became difficult and painful. She was able to eat and drink adequately so paracetamol 4x1,000 mg and pantoprazole 40 mg once daily was initiated. In week 5, the oral intake was decreased to a minimum because of esophageal pain. The serum creatinine increased and she started losing weight. By then, the family of the patient felt extremely concerned, feeling incapable of controlling the situation. As a consequence, they became angry with the patient for not consuming the food they prepared for her every day. When an endoscopy was performed, several mucosal defects were seen in the distal part of the esophagus; evidentially causing the pain. The patient was hospitalized and tube feeding and intravenous hydration was started. A pain physician was consulted and she started with intravenous analgesics. She was discharged after 1 week with oral analgesics and tube feeding. Within 3 weeks the esophagitis had recovered to AET grade 1 and she was able to eat and drink adequately so the tubefeeding could be discontinued.

Discussion

CCRT for locally advanced NSCLC is the treatment of choice despite its toxicity profile. AET is one of the most profound toxicity caused by this treatment but accepted because of survival benefits. The clinical implications of AET can vary but most often consist of pain, dysphagia, weight loss and dehydration. As a result, health related quality of life is likely to be (temporary) compromised. It is therefore recommended to optimize patient education and supportive care management for palliating symptoms.

Although research has been performed regarding pharmaceutical management of AET, there are no guidelines to address this problem. Demonstration has been made of the difference in pain in esophageal cancer patients receiving sucralfate or sodium alginate for AET following external beam and intracavitary RT (17). In the sucralfate group, patients had a significant relief of symptoms within 7 days of treatment and it was detected endoscopically that most ulcers had healed by 12 days of treatment. Patients receiving sodium alginate showed little improvement of symptoms and had persistent ulcers even after 4 weeks of therapy. However, although these results seemed promising, there was limited follow up with negative outcomes regarding sucralfate (18,19).

As seen above there is not yet a satisfactory golden standard in the management of acute oesophagus toxicity. Health care professionals should aim to inform patients about the risk of AET and start medication and nutritional interventions pro-actively.

Acknowledgements

None.

Footnote

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

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Cite this article as: Uyterlinde W. Overcoming toxicity-challenges in chemoradiation for non-small cell lung cancer. *Transl Lung Cancer Res* 2016;5(3):239-243. doi: 10.21037/tlcr.2016.05.03

Novel radiotherapy approaches for lung cancer: combining radiation therapy with targeted and immunotherapies

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Abstract: Targeted therapies and immunotherapies have quickly become fixtures in the treatment armamentarium for metastatic non-small cell lung cancer (NSCLC). Targeted therapies directed against epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) translocations, and ROS-1 rearrangements have demonstrated improved progression free survival (PFS) and, in selected populations, improved overall survival (OS) compared with cytotoxic chemotherapy. Immunotherapies, including checkpoint inhibitor monoclonal antibodies against programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1), have now also demonstrated improved survival compared with chemotherapy. The use of these novel systemic agents in non-metastatic patient populations and in combination with radiation therapy is not well defined. As radiation therapy has become more effective and more conformal with fewer toxicities, it has increasingly been used in the oligometastatic or oligoprogression setting. This has allowed improvement in PFS and potentially OS, and in the oligoprogressive setting may overcome acquired drug resistance of a specific lesion(s) to allow patients to remain on their targeted therapies. Molecularly targeted therapies and immunotherapies for patients with metastatic NSCLC have demonstrated much success. Advances in radiation therapy and stereotactic body radiotherapy, radiation therapy have led to combination strategies with targeted therapies among patients with lung cancer. Radiation therapy has also been combined with immunotherapies predominantly in the metastatic setting. In the metastatic population, radiation therapy has the ability to provide durable local control and also augment the immune response of systemic agents, which may lead to an abscopal effect of immune-mediated tumor response in disease sites outside of the radiation field in select patients.

Keywords: Abscopal effect; immunotherapy; lung cancer; radiation therapy; targeted therapy

Submitted Oct 02, 2015. Accepted for publication Oct 10, 2015.

doi: 10.3978/j.issn.2218-6751.2015.10.05

View this article at: <http://dx.doi.org/10.3978/j.issn.2218-6751.2015.10.05>

Role of radiation in early stage and locally advanced non-small cell lung cancer (NSCLC)

Definitive radiation therapy has been part of the standard of care for patients with locally advanced NSCLC for almost 5 decades. Combined modality therapy with chemoradiation became the preferred treatment of these patients based on multiple clinical trials showing improved survival (1,2).

Conventionally fractionated radiation therapy remains the standard, and attempts at dose escalation have failed to show a benefit in this patient population (3). Newer technologies such as intensity modulated radiation (4), image guided radiation therapy, and proton therapy (5-7) are increasingly being utilized or studied to lower rates of toxicity with combined modality therapy.

Table 1 Classes of targeted therapies in clinical use in metastatic non-small cell lung cancer

Target	Currently available targeted therapies
EGFR	Erlotinib
	Afatinib
	Gefitinib
	Cetuximab
ALK	Crizotinib
	Ceritinib
ROS1	Crizotinib
MET	Crizotinib
VEGF	Bevacizumab
	Ramucirumab

EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, ROS proto-oncogene 1; VEGF, vascular endothelial growth factor.

Surgical resection has been the standard of care for patients with stage I NSCLC with 5 years survival rates of approximately 60-70% (8,9). While patients determined to be medically inoperable have been treated in the past with standard fractionated radiotherapy, newer technologies within radiation therapy have led to the standardization of high dose, ablative hypofractionated therapy termed stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR) (10). SBRT has allowed for improved dose conformity, improved local tumor control, and superior overall survival (OS) when compared to conventionally fractionated radiotherapy (11,12). Based on the improved outcomes with SBRT and the increased utilization of this technology, interest in its use for medically operable patients has emerged. A recently published pooled analysis of two randomized trials comparing surgery and SBRT for stage I NSCLC demonstrated that SBRT was highly effective and had a limited toxicity profile, and that there was equipoise between the two treatment options (13).

SBRT has also begun to be used more frequently in patients with oligometastatic disease, including lung, liver, and bone metastases. Recent data has shown excellent control rates with encouraging progression free survival (PFS) in patients with oligometastatic NSCLC (14,15). Conventionally fractionated radiotherapy, in combination with chemotherapy, can also be considered in patients with oligometastatic disease not amenable to treatment with SBRT and may improve survival in a select subset of patients with minimal extrathoracic disease (16).

Targeted therapy for advanced NSCLC

With the discovery of molecular pathways that correspond with tumor progression and growth, numerous potential targets have been identified and explored for potential therapeutics for advanced NSCLC (*Table 1*).

Epidermal growth factor receptor (EGFR) is an essential part of the oncogenic growth pathway and is expressed at higher levels in some lung cancers. EGFR as a molecular target has shown promising results in advanced lung cancer. Monoclonal antibodies, such as cetuximab and panitumumab, and tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib, and afatinib, are available. Initial trials evaluating patients treated with cytotoxic chemotherapy either in combination or followed by EGFR pathway inhibitors without prior molecular mutation analyses demonstrated mixed results, although trials have generally demonstrated at least a benefit to PFS (17-23). Further subset analysis of many of these trials showed clear correlation between the presence of EGFR driver mutations and clinical benefit of these agents. This has led to the standardization of the use of EGFR TKIs in the first line setting for patients with EGFR mutations (24-30).

Vascular endothelial growth factor (VEGF) plays an essential part in tumor angiogenesis and is often expressed at higher rates in NSCLC, thus creating another molecular pathway target for therapy. The most well studied VEGF inhibitor in NSCLC, bevacizumab, has shown increased PFS and OS in patients with non-squamous NSCLC when added to standard cytotoxic chemotherapy (31-33). Ongoing trials are evaluating bevacizumab with other platinum combinations (NCT00150657, NCT00753909), as well as with other targeted agents such as erlotinib and ramucirumab (NCT01532089, NCT00257608, NCT00553800).

One of the most promising recent areas of new drug development in treatment of NSCLC has been anaplastic lymphoma kinase (ALK) inhibitors. These are targeted agents directed at the novel fusion oncogene echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase (EML4-ALK). The first available drug was crizotinib, an oral small-molecule inhibitor of ALK and c-Met tyrosine kinases. Crizotinib has shown favorable outcomes both in the second line setting, as well as in the primary treatment setting for patients that are positive for this rearrangement (34,35). Second generation TKI inhibitors of ALK include ceritinib and alectinib are undergoing investigation in national trials in ALK positive patients that have progressed, as well as the primary setting with pending

Table 2 Checkpoint inhibitors in clinical use or under development for advanced or metastatic non-small cell lung cancer

Monoclonal antibody	Target	FDA approved
Ipilimumab	CTLA-4 on T cells	Melanoma
Nivolumab	PD-1 on T cells	Lung cancer, melanoma
Pembrolizumab	PD-1 on T cells	Melanoma
BMS-936559	PD-L1 on tumor cells	No
MEDI4736	PD-L1 on tumor cells	No
MPDL3280A	PD-L1 on tumor cells	No
Lirilumab	Killer-cell immunoglobulin-like receptor (KIR) on NK cells	No
BMS-986016	Lymphocyte-activation gene 3 (LAG3) on tumor infiltrating lymphocytes	No

FDA, Food and Drug Administration; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed death receptor 1; PD-L1, programmed death ligand 1; NK, natural killer.

results (NCT02292550, NCT02393625, NCT02075840, NCT02271139). ALK inhibitors have also demonstrated efficacy in patients with chromosomal rearrangements of the gene encoding ROS1 proto-oncogene receptor tyrosine kinase, which occurs in 1-2% of patients with NSCLC (36).

Immunotherapy for advanced NSCLC

Utilizing the immune system as an effective oncologic tool to fight cancer has been the subject of preclinical and clinical research for several decades (37). Immunotherapy agents allow the immune system to recognize a patient's cancer cells as foreign, prompting an immune response resulting in tumor cell death and/or inhibition of tumor growth. Newer immunotherapy agents have been developed based on improved knowledge of the molecular process of the immune response, leading to a resurgence in investigative use of these agents for patients with NSCLC. Such checkpoint inhibitors include monoclonal antibodies to cytotoxic T-lymphocyte antigen 4 (CTLA-4) such as ipilimumab, as well as antibodies to programmed death receptor 1 (PD-1), such as nivolumab and pembrolizumab (Table 2).

CTLA-4 is responsible for regulation of early T cell activity. It becomes upregulated after antigen exposure and competes for binding with CD28, preventing the stimulatory signal needed for T cell activation. Thus, inhibition of this receptor allows T cell activation after tumor antigen presentation. PD-1 is also upregulated on T cells, but it is thought to play a role further down the immune response pathway within the tumor microenvironment. Binding of PD-1 to programmed death ligand 1 (PD-L1) leads to T cell inactivation, and antibodies

to PD-1 allow activation to proceed at the site of direct anti-tumor immune response.

The majority of data for use of these newer immunotherapy agents in NSCLC have been studied in advanced, stage IV patients. Ipilimumab was developed as an IgG1 CTLA-4 monoclonal antibody and was originally investigated in metastatic melanoma. A phase II randomized trial combining ipilimumab with standard first line chemotherapy in patients with stage IIIB-IV NSCLC showed improvement of PFS with the addition of ipilimumab (38). Subset analysis showed that patients with squamous cell histology benefitted primarily from the addition of ipilimumab, prompting an ongoing phase III trial that is comparing standard first line chemotherapy with carboplatin and paclitaxel with or without the addition of ipilimumab in patients with advanced squamous cell NSCLC. Additional trials are evaluating its effectiveness in combination with other targeted or immunotherapy agents (39).

Anti PD-1 antibody agents have been more commonly studied in patients with progressive metastatic NSCLC and showed promising results with prolonged tumor responses (40). Based on the recently published data from the CheckMate 017 and 063 trials in 2014, nivolumab has now received Food and Drug Administration (FDA) approval for treatment of advanced squamous cell NSCLC. Checkmate 063 was a single arm phase II trial in patients that had progressed after at least two prior systemic treatments. Nivolumab achieved an encouraging 1 year survival rate of 41% in these heavily pretreated patients (41). The follow up phase III trial, CheckMate 017, randomized patients with metastatic squamous cell NSCLC who had progressed after doublet chemotherapy to nivolumab or and docetaxel. The trial was stopped early due to superior OS in the nivolumab arm with a median survival of 9.2 vs. 6 months

in the docetaxel arm ($P=0.00025$). Nivolumab also showed a more favorable toxicity profile compared with docetaxel (42). Additional phase III trials are currently evaluating pembrolizumab monotherapy in both the first line and second line setting for advanced and metastatic NSCLC (NCT02220894, NCT02142738) (38).

Targeted therapy with radiation therapy for localized NSCLC

Many targeted therapies have been integrated into the treatment of localized NSCLC. While the data are much more limited than for the metastatic setting, targeted therapies have been used in combination with or concurrently with radiation therapy. The majority of this data are in conjunction with radiation therapy in the setting of locally advanced NSCLC classically treated with concurrent chemotherapy and radiation.

Preclinical data have shown biologic rationale for combining EGFR inhibitors and radiation therapy. Cetuximab has been combined with chemotherapy and radiation in treatment of locally advanced NSCLC in both phase II and phase III trials (3,43,44). In two sequential Radiation Therapy Oncology Group (RTOG) trials, cetuximab was combined with carboplatin/paclitaxel and radiation therapy for stage IIIA/IIIB lung cancer. While the median survival (22.7 months) and 24-month OS (49.3%) achieved in the phase II study (RTOG 0324) of cetuximab and concurrent chemoradiation were longer than any previously reported by the RTOG (43), the randomized phase III trial RTOG 0617 failed to show a benefit to the addition of cetuximab to chemoradiation in an unselected population (3). Among all patients, median OS in patients randomized to cetuximab was 25.0 *vs.* 24.0 months among those not receiving cetuximab ($P=0.29$). However, in a planned analysis of the association of EGFR expression and outcome, among patients with an EGFR H score of 200 or higher, cetuximab use was associated with improved OS (42.0 *vs.* 21.2 months, $P=0.032$) (3).

Gefitinib and erlotinib have also been integrated into both the concurrent chemoradiation setting, as well as a maintenance therapy after chemoradiation for locally advanced NSCLC (45-47). Again, phase III trials have failed to show a benefit to these agents in all subsets of patients, but they have shown improved outcomes in patients who had evidence of EGFR amplification or EGFR mutation, suggesting that in selected patients, these drugs may prolong PFS or OS in combination with chemotherapy

and radiation therapy for non-metastatic patients. Newer studies are evaluating the use of these agents in patients with confirmed mutations (NCT01391260, NCT01822496, NCT02277457) (38).

Another area of clinical interest combining radiation and targeted therapy has been in the limited or oligometastatic setting. While the definition of oligometastatic has varied in the clinical literature, there has been increased use of local therapies for patients with limited sites of metastatic disease, especially as the ability to deliver effective local therapies with less morbidity has improved. Given the encouraging local control and limited toxicity profile of SBRT in both the lung and other organs commonly afflicted with metastasis from lung cancer, this remains an active area of research in treating patients with limited oligometastatic disease in combination with targeted agents. One recent published phase II trial showed encouraging results for PFS in advanced NSCLC patients with six or fewer sites of metastatic disease when they were treated with local SBRT to these sites in combination with second line erlotinib (7). Other active studies are similarly looking at this patient population in combination with other targeted as well as immunotherapeutic agents (NCT02450591, NCT0208672, NCT02444741).

As in the oligometastatic setting, the use of radiation therapy can be considered in the oligoprogression setting among patients being treated with TKIs for metastatic NSCLC. While patients with stage IV NSCLC and EGFR mutation or ALK rearrangement have achieved excellent PFS with targeted therapy, disease progression often occurs within a year of therapy initiation. While initial progression of EGFR- or ALK-directed therapy can be diffuse, many patients can have oligoprogression, or limited sites of progression, potentially due to acquired resistance from evolutionary selection on molecularly diverse tumors in which tumor clones in some sites of metastasis but not others develop resistance. Systemic options for such patients include increasing the dose of the targeted therapy they are progressing on, switching to another next-line targeted therapy, switching to cytotoxic chemotherapy, or adding chemotherapy to the targeted therapy (48). However, several groups have recently demonstrated that radiation therapy or other local therapies to sites of oligoprogression can also be considered and can achieve durable local control of the sites of progression and also allow for patients to be maintained on their existing TKI, thus saving alternative or next-line systemic therapy options for subsequent disease progression (49,50).

Anti-angiogenesis agents typically targeting VEGF have become standard treatment components of therapy for advanced NSCLC. Bevacizumab has been studied in combination with radiation therapy, but this combination has shown a high incidence of tracheoesophageal fistula formation when given concurrently, especially among patients with squamous cell carcinoma and centrally located tumors being irradiated (51).

Given the favorable results in advanced lung cancer, integration of ALK inhibitors into the setting of locally advanced NSCLC has already entered ongoing randomized phase II trials, including NRG/RTOG 1306/NCT01822496, which is evaluating erlotinib and crizotinib as induction therapy followed by standard chemoradiation in patients with confirmed EGFR mutation or EML4-ALK fusion rearrangement, respectively (39).

Immunotherapy with radiation therapy for NSCLC

Although there is limited data to date combining radiation therapy and immunotherapy, this combination has the ability to achieve a synergistic therapeutic effect (52,53). As ionizing radiation can increase the production and presentation of tumor antigens, it can serve to augment the antitumor immune responses achieved by checkpoint inhibitors (54). Radiation therapy can augment immunomodulation by bolstering cytotoxic T-lymphocyte activity (53) and reduce myeloid-derived suppressor cells (55), allowing for synergism with checkpoint inhibitors.

SBRT may be the radiotherapy modality most optimally combined with immunotherapy since it can achieve a more robust immune response than conventionally fractionated radiotherapy. SBRT has been shown to induce cellular expression of major histocompatibility complex (MHC) I, inflammatory mediators, costimulatory molecules, heat shock proteins, immunomodulatory cytokines, adhesion molecules, and death receptors, all of which can enhance antitumor immune responses of systemic therapy (56).

There have been a number of reports in which a distant tumor mass regresses following the administration of radiation therapy before or after treatment with immunotherapy, known as the abscopal effect (57-59). In addition to the abscopal effect, radiation therapy may also allow for immune activation that leads to a more complete or accelerated clearance of the irradiated tumor, or sterilization of microscopic metastasis that were not clinically apparent at the time of irradiation. Aside from case reports, a number

of prospective clinical trials have been completed that have combined anti-CTLA-4 therapy and radiotherapy for melanoma (60) and prostate cancer (61) with promising results. A phase I/II study in metastatic castration resistant prostate cancer combining ipilimumab in combination with radiation therapy showed 50% of patients having a decline in prostate-specific antigen (PSA) with one complete response (60). A phase I trial combining ipilimumab and radiation in melanoma showed a response rate of 18% and PFS of 3.8 months prompting further investigation into this combination in the clinical setting (62). To date, no prospective study combining radiation therapy with anti-CTLA-4, anti-PD-1, or anti-PD-L1 therapy has been completed for lung cancer.

Future directions

Targeted therapy and immunotherapy have become pillars of lung cancer treatment. As we gain a greater understanding of the molecular basis of lung cancer, additional targeted agents will become part of standard practice to expand the role beyond the currently limited proportion of lung cancer patients with a known targetable mutation or translocation. Additionally, with increasing knowledge of acquired mutations, second- and third-line targeted agents will become standard options over salvage cytotoxic chemotherapy offering the promise of greater effectiveness and less toxicity. Cooperative group studies combining targeted agents and radiotherapy for non-metastatic patients are ongoing (NCT01822496).

Similarly, immunotherapies will become more entrenched as standard therapy for second-line NSCLC and will be investigated in the first line setting. Combination therapies will increasingly be the subject of investigation, including the inhibition of both CTLA-4 and PD-1, or the use of an immunotherapy agent with a targeted therapy or with a cytotoxic chemotherapy. Toxicities to such combinations, however, may prove prohibitive.

While there is much excitement around the phenomenon of a radiotherapy-induced anticancer immune response and combining radiation therapy with immunotherapy, numerous questions remain before this combination can be exported to routine clinical practice. Additional research is needed to determine if conventionally fractionated irradiation, multi-fraction SBRT, or single fraction SBRT is most effectively combined with immunotherapy, and how radiotherapy and immunotherapy should be sequenced. Like with combination systemic therapies, combining

radiotherapy with such novel immunotherapies and systemic therapies may result in overlapping toxicities of radiation therapy and immunotherapy. In addition to the immune modulators and checkpoint inhibitors discussed in this manuscript, additional ways to provide tumor-associated antigen to the immune system that can be combined with radiotherapy are currently being investigated, including recombinant vaccines, tumor lysates, and synthetic peptides. While early results are promising, studies combining radiation therapy with immunotherapy warrant careful consideration of toxicity and safety.

Acknowledgements

None.

Footnote

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

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Cite this article as: Simone CB 2nd, Burri SH, Heinzerling JH. Novel radiotherapy approaches for lung cancer: combining radiation therapy with targeted and immunotherapies. *Transl Lung Cancer Res* 2015;4(5):545-552. doi: 10.3978/j.issn.2218-6751.2015.10.05

Integrating immunotherapy into chemoradiation regimens for medically inoperable locally advanced non-small cell lung cancer

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Contributions: (I) Conception and design: All authors; (II) Administrative support: SK Jabbour; (III) Provision of study materials or patients: SK Jabbour; (IV) Collection and assembly of data: SK Jabbour, CB Simone 2nd; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: For patients with inoperable stage II–III non-small cell lung cancer (NSCLC), the backbone of curative intent therapy is concurrent chemoradiotherapy (CRT). As checkpoint inhibitors have shown clinical benefit in the setting of metastatic NSCLC, additional study is necessary to understand their role in patients receiving CRT. When integrating immunotherapy with radiotherapy (RT) for cure, clinicians will need to consider synergy, timing, doses, and safety among the combination of therapies. This article seeks to review data evaluating interactions, temporal sequencing, fractionation, and overlapping toxicity profiles of thoracic chemoradiation and immunotherapy.

Keywords: Immunotherapy; chemoradiation; non-small cell lung cancer (NSCLC); PD-1; PD-L1

Submitted Mar 26, 2017. Accepted for publication Mar 28, 2017.

doi: 10.21037/tlcr.2017.04.02

View this article at: <http://dx.doi.org/10.21037/tlcr.2017.04.02>

Introduction

For patients with inoperable stage II–III non-small cell lung cancer (NSCLC), the backbone of curative intent therapy is concurrent chemoradiotherapy (CRT). The supportive evidence for the use of combined CRT is rooted in several decades of methodical clinical studies that established the superiority of concurrent CRT compared to either modality alone or sequential delivery of chemotherapy followed by radiotherapy (RT) (1-5). The customary platform for localized and inoperable NSCLC consists of concurrent chemoradiation with a platinum-based doublet and 60 Gy of RT delivered daily over 6 weeks followed by consideration of two cycles of consolidative chemotherapy, particularly for carboplatin and paclitaxel regimens (6,7). Although consolidative chemotherapy was not found to demonstrate an obvious survival benefit for inoperable, locally advanced NSCLC (8,9), its incorporation into RTOG 0617 has led to its acceptance as the de facto standard of care (7). Despite

its acceptance as a curative intent treatment, concurrent CRT results in relatively meager treatment outcomes with median survival rates of 20–28 months and 5-year overall survival (OS) rates of 15–20%.

The advent of novel immunotherapy agents affords patients and clinicians therapeutic modalities to improve patient longevity and avenues to study innovative combinations of therapies (10-13). Incorporation of immunotherapy with standard therapy provides the potential to build upon the gains of the well-established regimen of CRT for inoperable NSCLC. Since checkpoint inhibitors have shown clinical benefit in the setting of metastatic NSCLC, additional study will be necessary to understand their role in combined modality CRT. When integrating immunotherapy with RT for cure, clinicians will need to consider synergy, timing, doses, and safety among the combined therapies. This article seeks to review data evaluating interactions, temporal sequencing, fractionation, and overlapping toxicity profiles of CRT and

immunotherapy.

Immune modulation in the setting of RT

Local ionizing radiation can interact with the host's immune system by increasing the tumor antigen specific effector cells that traffic to a tumor. In a study comparing xenografts with B16-F0 tumors, irradiated mice (treated with 15 Gy) had greater ability to present tumor antigens and specific T-cells and tumor infiltrating lymphocytes than non-irradiated mice (14). In melanoma murine models, tumor control increased with the size of the RT dose as did tumor-reactive T cells, but a dose of 7.5 Gy per fraction proved to be the regimen with the optimal tumor control and tumor immunity with the lowest number of T-regulatory cells (T-regs) (15).

RT modulates the immune system and can help to mount an immune response that can result in immunogenic cell death. Radiation releases tumor antigens and facilitates tumor antigen release by dendritic cells (DC) and cross-complementation on major histocompatibility complex-1 (MHC-1) (16). RT potentiates calretinin's exposure on the cell surface and release of ATP and high mobility group box 1 (HMGB1), which seems to be required for DC activation and immune priming against malignant cells (17). Therefore, RT also acts as an in-situ tumor vaccine and may immunize the patient against their neoplasm and can provide immunologic memory which may endure for the host's lifetime (18,19).

RT also provides a pro-immunogenic effect on the tumor microenvironment (18). RT elicits activation of both innate and adaptive immunity (20), and these immune responses are potentiated by the cellular damage caused by RT and the cascade of interleukin-1 β (IL-1 β), tumor necrosis-factor- α (TNF- α), and chemokine (C-C-C motif) ligand 16 (CXCL16), MHC molecules, adhesion molecules and death receptors (21). RT also can reprogram macrophage differentiation to an iNOS+/M1 phenotype that orchestrates effective T cell immunotherapy (18,22).

The interaction of RT and checkpoint inhibitors or other immunotherapies may lead to an abscopal effect whereby after the administration of RT to one location, a non-responding systemic tumor then displays diffuse systemic response at distant sites from the site of irradiation. This concept has gained much attention in the setting of metastatic melanoma patient who had been maintained on ipilimumab with relatively stable disease subsequently received stereotactic body RT to an enlarging paraspinal

mass and was found to have response at their other sites of distant metastases. The authors suggested that the tumor was resistant to T cell mediated antitumor effects until the delivery of RT (23). T cells are thought to be a driver for the abscopal effect, which may require Flt-3 ligand as mice bearing tumor in both flanks responded in both flanks despite irradiation of only one flank when Flt-3 was available (24). This abscopal effect has been demonstrated on multiple occasions but is thought to be relatively infrequent, and no reliable method has been discovered to reproducibly harness these potent series of events clinically.

PD-1 and its interaction with RT

Programmed cell death-1 is an immune checkpoint inhibitory receptor and facilitates immune escape (25). PD-1 primarily curbs the activity of T cells in the periphery during chronic inflammation, infection or cancer and limits autoimmunity. When PD-1 interacts with its ligand PD-L1, it can inhibit T cell growth, survival, and effector function, such as cytokine release and cytotoxicity (26), and leads to tumor specific T cell apoptosis (27), stimulates the differentiation of CD4+ T cells into T-regs (28) and allows for the resistance of tumor cells to cytotoxic T cell (CTL) attack (29).

Inhibition of PD-1, and likely PD-L1, improves tumor rejection. Polyclonal antibody against PD-L1 can promote tumor rejection in models (29). Since PD-1 is expressed directly on tumor surfaces, this is an attractive target for immune-mediated responses. PD-1 blockade can allow for tumor rejection and immune-mediated signaling to allow the immune system to attack the tumor. PD-1 expression is generally increased in tumors with a higher non-synonymous mutational burden in tumors and is associated with improved responses and durable clinical benefit with longer progression-free survival in NSCLC (30). Given the high mutational burden that is often seen in smokers who develop NSCLC, PD-1/PD-L1 inhibition appears to be a logical combination.

Blockade of PD-L1 improves T cell responses leading to tumor rejection (31). PD-L1 can be upregulated in the tumor microenvironment after RT in murine models. The addition of anti-PD-L1 therapy can improve the efficacy of RT through a CTL-dependent mechanism. This combination also reduced tumor-infiltrating myeloid-derived suppressor cells that contribute to altering the tumor microenvironment (32).

Importantly, the interaction of stereotactic RT can

Table 1 Trials of PD-1 or PD-L1 agents combined with chemoradiation for NSCLC

Clinical trial title (phase of trial)	NCT identification (number/institution/status)
Pembrolizumab, Paclitaxel, Carboplatin, and Radiation Therapy in Treating Patients With Stage II-III Non-Small Cell Lung Cancer (I)	NCT02621398/Rutgers Cancer Institute of New Jersey, University of Pennsylvania, Yale/recruiting
Consolidation Pembrolizumab Following Chemoradiation in Patients With Inoperable/Unresectable Stage III NSCLC (II)	NCT02343952/Hoosier Oncology Group/active, not recruiting
A Global Study to Assess the Effects of MEDI4736 Following Concurrent Chemoradiation in Patients With Stage III Unresectable Non-Small Cell Lung Cancer (PACIFIC) (III)	NCT02125461/AstraZeneca/active, not recruiting
Nivolumab COnsolidation with Standard First-line Chemotherapy and Radiotherapy in Locally Advanced Stage IIIA/B Non-Small Cell Lung Carcinoma (NICOLAS) (II)	NCT02434081/European Thoracic Oncology Platform/recruiting
Cisplatin and Etoposide Plus Radiation Followed by Nivolumab/Placebo for Locally Advanced NSCLC (III)	NCT02768558/ROG Foundation, Inc./recruiting
MPDL3280A with Chemoradiation for Lung Cancer (II)	NCT02525757/MD Anderson Cancer Center/recruiting

Ongoing trials incorporating immunotherapy with definitive chemoradiation for inoperable NSCLC.

augment antigen-specific PD-1 mediated antitumor responses by inducing a more robust immune response and cross-presentation of tumor antigen, which was studied in melanoma and breast cancer models (33). In those models, RT resulted in the development of antigen-specific T cell and B cell-mediated immune responses. These immune stimulating effects of RT were increased when RT was combined with anti-PD-1 therapy or regulatory T cell depletion and resulted in improved local control of the tumor.

As discussed in other articles in this series, anti-PD-1 and anti-PD-L1 therapies have shown clinical activity for NSCLC alone and in combination with chemotherapy. Since the clinical effect of anti-PD-1/anti-PD-L1 therapies is evident without the incorporation of RT, it is plausible that the incorporation of RT may provide combinatorial, abscopal or synergistic effects.

Timing, dose, fractionation of immunotherapy with chemoradiation

To date, clinicians have related many of the abscopal responses to hypofractionated irradiation regimens, often with stereotactic body radiotherapy (SBRT), also termed stereotactic ablative radiotherapy (SABR). Dewan et al. evaluated three RT fractionation schemes: 20 Gy \times 1, 8 Gy \times 3 or 6 Gy \times 5 with or without CTLA blockade. CTLA blockade alone was ineffective, but when combined with any of the RT regimens, growth delay was seen. Abscopal effects were evident with the combination of the fractionated RT

designs (34). Clinically, abscopal effects have been seen with 8 Gy \times 3, 6 Gy \times 5, and 9.5 Gy \times 3 fractions (23,35,36). The greatest difference occurred for patients with 8 Gy \times 3, and 80% of tumors outside the field regressed (16). Lower RT doses may cause reprogramming of macrophages toward an iNOS+/M1 phenotype, enabling them the ability to allow tumor rejection (37).

Also, concurrent platinum and RT cause calretinin translocation from dying tumor cells at dosages tested in a dose-dependent manner. Calretinin translocation increased due to platinum but remained stable after adding RT. Nevertheless, platinum and RT cause release of HMGB1 from dying tumor cells. When RT was combined with paclitaxel, adding RT caused immunogenic cell death (18).

A study by Gulley *et al.*, demonstrated the possible efficacy of standard radiation fractionation of 1.8–2 Gy per day in combination with a poxviral vaccine. T cell responses were seen in the tumor antigens and not in the vaccine, suggesting irradiation promoted the activation of T cells (16,38). Therefore, the combination of standard fractionation CRT and immunotherapy may be effective when they are used together.

Ongoing trials will help to elucidate the role and timing of PD-L1 or PD-1 blockade for inoperable NSCLC treated with definitive chemoradiation (*Table 1*).

Additional immunotherapy combinations

For locally advanced NSCLC, other agents have been

investigated, including tecemotide (L-BLP25), a mucin 1 (MUC1) specific agent that induced T cell responses to MUC1. The phase III START trial was a double-blind phase III trial that randomly assigned 1,006 subjects to tecemotide and 507 to placebo. Median overall survival (OS) was 25.6 months with tecemotide *vs.* 22.3 months with placebo (HR 0.88, 95% CI: 0.75–1.03, P=0.123). In patients who received prior concurrent CRT, median OS for those who received tecemotide was 30.8 months compared to 20.6 months for the control group (HR 0.78, P=0.016), whereas patients who received sequential CRT did not benefit in terms of OS (39,40). In the group of patients who received prior CRT, high soluble MUC1 and antinuclear antibodies correlated with tecemotide benefit (41). However, in a subsequent study by Katakami *et al.*, which randomized Japanese patients (n=172) with stable or clinical responses after CRT to receive adjuvant tecemotide *vs.* placebo, no apparent trend toward increased OS or other secondary endpoint with tecemotide was observed (42).

Additionally, study of GV1001, a telomerase peptide vaccine, was administered after CRT in a phase I/II trial of 23 patients. A GV1001-specific immune response developed in 16/20 evaluable patients and long-term immunomonitoring showed persisting responses in 13 patients. Immune responders demonstrated a median progression-free survival of 19 months compared to 3.5 months for nonresponders (P<0.001). Responders all harbored durable GV1001-specific T-cell memory responses with high IFN γ , and low IL-4 and IL-10 levels (43,44).

Toxicities of immunotherapy overlap with RT side effects

Administration of thoracic RT places patients at higher risk of radiation-induced pneumonitis, and the clinical presentation is similar to immunotherapy-induced pneumonitis with dry cough, fever, dyspnea, and tachycardia. Urgent initiation of steroid therapy is often required. A study evaluating 915 patients who were treated with PD-1/PD-L1 antibody demonstrated that 43 patients developed pneumonitis (about 5% of patients). Pneumonitis was more likely to occur when anti-PD-1/anti-PD-L1 and another simultaneous immunotherapy were administered, such as concurrent CTLA-4 therapies. Pneumonitis is a toxicity of variable onset clinically, and in the aforementioned study, it ranged from 9 days to 19.2 months (45). Concern for a pneumonitis requires urgent evaluation with imaging and often rapid

initiation of steroids to avoid severe and potentially life-threatening respiratory compromise.

Another complication that can occur with both RT and immunotherapy is myocarditis. Unlike pericarditis that can occur in the acute or subacute setting, radiotherapeutic injury to the myocardium is thought to be a delayed effect with long-term toxicities such as coronary artery disease and valvular injury. In contrast, fulminant cases of myocarditis from immunotherapy have been described, particularly with the combination of nivolumab and ipilimumab. The incidence of fatal myocarditis with nivolumab alone is <0.01% and with dual nivolumab and ipilimumab is 0.17%. The incidence of any myocarditis with single-agent nivolumab is 0.06% compared to 0.27% with dual agent therapy. In post-mortem examination of the cardiac tissue of immune checkpoint mediated myocarditis, increased expression of PD-L1 was found in the injured myocardium of patients, consistent with the upregulation of myocardial PD-L1 studies in mice. Investigators have hypothesized that PD-L1 upregulation in the myocardium is a cytokine-induced cardioprotective mechanism that is abrogated by immune checkpoint blockade (46).

Therefore, combinatorial therapy of CRT and immunotherapy must be approached with caution and careful clinical evaluation in prospective clinical trials.

Acknowledgements

None.

Footnote

Conflicts of Interest: Dr. Jabbour has research funding from Merck Sharp & Dohme. The other authors have no conflicts of interest to declare.

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Cite this article as: Jabbour SK, Berman AT, Simone CB 2nd. Integrating immunotherapy into chemoradiation regimens for medically inoperable locally advanced non-small cell lung cancer. *Transl Lung Cancer Res* 2017;6(2):113-118. doi: 10.21037/tlcr.2017.04.02

Uncovering the immune tumor microenvironment in non-small cell lung cancer to understand response rates to checkpoint blockade and radiation

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: The study of immunology has led to breakthroughs in treating non-small cell lung cancer (NSCLC). The recent approval of an anti-PD1 checkpoint drug for NSCLC has generated much interest in novel combination therapies that might provide further benefit for patients. However, a better understanding of which combinations may (or may not) work in NSCLC requires understanding the lung immune microenvironment under homeostatic conditions and the changes in that microenvironment in the setting of cancer progression and with radiotherapy. This review provides background information on immune cells found in the lung and the prognostic significance of these cell types in lung cancer. It also addresses current clinical directions for the combination of checkpoint inhibitors with radiation for NSCLC.

Keywords: Anti-CTLA4; anti-PD1; immunotherapy; radiotherapy; non-small cell lung cancer (NSCLC)

Submitted Nov 19, 2016. Accepted for publication Mar 21, 2017.

doi: [10.21037/tlcr.2017.03.06](https://doi.org/10.21037/tlcr.2017.03.06)

View this article at: <http://dx.doi.org/10.21037/tlcr.2017.03.06>

The lung as an immune organ

Because the lungs are constantly exposed to foreign pathogens and particulates, well-established mechanisms are in place to quickly eliminate these and other types of invaders. First, the upper respiratory tract is coated with mucus that contains many antimicrobial compounds. This mucus is constantly secreted by goblet cells and expelled by ciliated epithelial cells (1). Epithelial cells that line the respiratory tract also express pattern recognition receptors (PRRs) that recognize molecular patterns associated with pathogens and other dangerous particles or cells; not only

can these cells modulate the response to infection through various pathways, they also can recognize, take up, and kill pathogens (2,3). These epithelial cells also direct immune responses through cytokine recognition and secretion (2).

The next line of defense in the lung rests in immune cells. Tissue-resident alveolar macrophages are readily available for phagocytosis and for clearing debris. In fact, 95% of the airspace leukocytes are alveolar macrophages; very few are lymphocytes or neutrophils (4). Various cells in the lung, including alveolar macrophages, dendritic cells (DCs), and granulocytes also express PRRs that

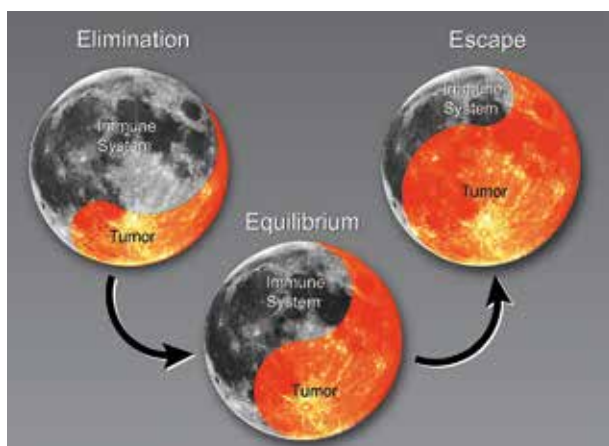


Figure 1 The interplay between the immune system and the tumor. There is a battle between the tumor and immune system; certain immune cells are able to attack the tumor, while the tumor has developed various ways to evade the immune system. Typically, tumors are eliminated by immune surveillance (elimination). However, some tumors are capable of pushing back against the immune system (equilibrium), where they eventually develop various mechanisms to stop immune-mediated tumor killing (escape). In NSCLC, the myeloid cells appear to be playing a major role in this process. Radiation may be able to push the immune system back to elimination. NSCLC, non-small cell lung cancer.

trigger immune responses to perturbation of homeostatic conditions. This allows quick recruitment of other immune cells to the lung that can mount an effective response and clear pathogens that may be present.

An important cell type residing in the lungs are lymphocytes. In a study of the prevalence of various lymphocyte populations in the lung, Wong *et al.* used cytometry by time-of-flight (CyTOF) to interrogate subsets of lymphocytes identified by surface and intracellular protein expression from healthy donors (5). CD8⁺ T cells and CD4⁺ T cells were the most prevalent subtypes in lung tissue, although natural-killer (NK) cells and NK T cells were also present. Very few B cells were found in the lungs. In vitro stimulation of lung cultures to detect intracellular cytokines revealed that the most prevalent CD4⁺ subset in the lung was T helper I [Th1; expresses interferon-gamma (IFN- γ)], although T helper II [Th2; interleukin (IL)-4 expressing] and regulatory T cell (Treg, IL-10 expressing) were detected at low levels. Interestingly, granulocyte macrophage colony-stimulating factor (GM-CSF) expression by the CD4⁺ T cells in the lung was also very

high and overlapped with IFN- γ expression; production of GM-CSF by T cells has been shown to influence DC maturation (6) and drive immune disorders, specifically multiple sclerosis (7).

Immunological changes during cancer development

The progression of cancer with regard to the immune system has been described in three stages: elimination, equilibrium, and escape (8,9). During the elimination phase, the immune system actively attacks cancerous cells (*Figure 1*). The tumor reaches equilibrium with the immune system before it eventually escapes immune surveillance. At that stage, the tumors begin to grow. The following sections describe changes in the immune system that result in clinically relevant NSCLC, specifically the current understanding of immune cell populations linked to cancer and cancer outcomes derived from preclinical models, in silico sequencing analysis, and clinical evidence.

Preclinical studies of immunologic changes in lung cancer

Numerous preclinical studies have focused on the lung tumor microenvironment (TME) in efforts to reveal how tumors escape immune surveillance. In a study of the Lewis lung carcinoma (LLC) model of NSCLC, interactions of the death receptor Fas on tumor cells with its ligand did not promote apoptosis, but rather caused recruitment of myeloid-derived suppressor cells (MDSCs) to the tumor through secretion of prostaglandin E2 (PGE2) (10). PGE2 has been well studied in the context of inflammation and cancer promotion (11). That study also showed that forced overexpression of Fas on the tumor cells caused enhanced MDSC and Treg infiltration into the tumors, and depletion of MDSCs through an anti-Gr1 antibody was found to delay tumor growth. Another group also found that Fas overexpression in the LLC model led to enhanced tumor growth (12), noting that MDSC-like cells accumulated in response to cigarette smoke but that those cells did not acquire suppressive functions until after a tumor had formed (13). Drugs targeting MDSCs like gemcitabine or arginase inhibitors may facilitate T cell infiltration in the lung TME. Suzuki *et al.*, also working with the LLC model, found that gemcitabine led to reduced numbers of MDSCs in the spleen (14), and the loss of MDSCs was reported to increase tumor growth delay in mice bearing both small and large AB12 mesothelioma tumors.

Other factors apart from PGE2 influence inflammation in preclinical lung cancer models. Kim *et al.* (15) found that tumor cells secreted an extracellular matrix protein called versican, which stimulated toll-like receptor (TLR) 2 on macrophages and drove the production of pro-inflammatory cytokines, specifically IL-6 and tumor necrosis factor-alpha (TNF- α). This effect was abrogated when TLR2 was knocked out in the mice; interestingly, those mice had fewer lung and liver tumors as well as prolonged. Additionally, blocking monocyte chemoattractant protein-1, also known as CCL2, can inhibit tumor growth and spontaneous metastases (16). Upon CCL2 blockade, macrophages were found to shift away from a pro-tumor phenotype, and this antitumor effect was dependent on CD8+ T cells; even though the percentages of CD8+ T cells did not increase, the expression of the activation markers CD25 and 41BB on those cells doubled.

The effect of neutrophils on the lung TME has been studied with a lung cancer model based on methylcholanthrene and hydroxytoluene exposure. In one study, depletion of Ly6G+ neutrophils led to considerable reductions in the number of tumor sites (17). However, once a tumor had formed, neutrophil depletion did not affect the growth of that tumor. These results suggest that neutrophils may be important for tumor initiation and metastasis but not tumor growth.

Overall, these studies suggest that tumors are fully capable of recruiting and polarizing myeloid cells to block adaptive immunity. They also imply that chronic inflammation may be an important factor driving the accumulation of such cells in the lung TME.

In silico methods of investigating immune-cell changes in lung cancer

Technical constraints have impeded in-depth investigations of the TME in humans over the past decade, including difficulties in identifying and studying specific types of cells in a tumor owing to intratumoral heterogeneity and identifying functional differences such as different patterns of gene expression in specific cell subsets, largely because of the inability to resolve gene expression differences at the level of individual cells or cell types (18-20). However, recent advances in single-cell genomics, transcriptomics and computational techniques have facilitated investigations of the nature of intratumoral heterogeneity in cell type and in the functional behavior of infiltrating cells (i.e., levels of PD-1 expression on the cell surface of CD4+ T cells). Much of the work in single-cell 'omics' has been limited

to investigations of clonal diversity and tumor evolution at the level of the tumor genome, with relatively limited effort applied to evaluating non-tumor cells (19-21).

One novel way of distinguishing the individual expression profile of cell types in tumor samples is by applying a linear support vector regression-based algorithm; this approach was recently proposed and tested on existing tumor data from more than 18,000 patients from The Cancer Genome Atlas (TCGA) and the Encyclopedia of DNA Elements (ENCODE) (22,23). This method quantifies the composition of cell types by using gene expression data from tumor samples by inferring cellular compositions based on levels of expression from sets of genes based on known transcriptome profile of purified cell types.

The investigators who pioneered this algorithm evaluated tumor-infiltrating immune cell subpopulations across a range of solid tumor cell types and found that that the predominance of specific subtypes of immune cells seem to be positive predictors of outcome (23). Specifically, in lung adenocarcinoma they found that an abundance of inactivated mast cells, inactivated CD4 memory T cells, and naïve and memory B cells and plasma cells was strongly associated with favorable prognosis. On the other hand, an abundance of polymorphonuclear cells and other cells of myeloid origin was strongly associated with unfavorable prognosis. Unexpectedly, the presence of activated CD4+ memory T cells was also strongly associated with poor prognosis. In lung squamous cell carcinoma, most myeloid populations seemed to confer an unfavorable prognosis, as did memory B cells and resting CD4 memory T cells. However, the presence of activated DCs was favorable, as were activated CD4 memory, CD8, and gamma delta T cells. In both subsets of lung cancer, the presence of inactivated mast cells was associated with favorable prognosis.

Other preclinical investigations are undergoing, such as deeper phenotyping—for instance, are there specific subsets of CD4 T helper cells whose presence in tumors improve cancer outcomes? How does the memory status of helper T cells affect the TME? Does the TME differ based on patient age? Some evidence exists to suggest that inflammation increases with advanced age and is mediated through MDSCs (24). Further studies of the lung TME will probably help to answer these questions.

Clinical correlates of immune-cell subpopulations in lung cancer

Many groups have attempted to profile immune-cell

subpopulations in patients with lung cancer by using techniques such as tissue microarray and immunohistochemical staining. Most such studies were done with resected tumor samples that had later been stained to evaluate immune subpopulations and their correlation with survival after surgery. Studies involving blood-based biomarkers have included samples from patients treated with a variety of modalities.

Myeloid cells

Given the prevalence of macrophages in the lung, many have investigated their role as either the tumor-suppressing (M1) or the tumor-promoting (M2) macrophage subtypes. An excellent review of tumor-associated macrophages (TAMs), their polarization, and their localization in lung cancer with regard to prognosis (25) suggested that infiltration of macrophages into tumor islets or nests (26-29) or M1 polarization (29,30) correlate with better survival in patients with lung cancer, whereas TAM density (31,32), their presence in the tumor stroma (26,27,33), and/or M2 polarization (34,35) correlate with worse survival. Other groups have found that IL-10 expression (M2-related) in TAMs (but not in tumors) at the protein level was associated with worse overall survival (36) and high IL-10 mRNA levels in TAMs were associated with tumor invasion (37). Although some studies found no correlation between TAMs and tumor progression (38-40), most have implicated TAMs in lung cancer progression.

Tumor infiltration by TAMs may not be the only relevant macrophage-related factor in lung cancer prognosis. One group showed that alveolar macrophages (obtained through bronchoalveolar lavage from patients with lung cancer) had reduced phagocytic capability (41). Incubation of alveolar macrophages with PGE2 also led to decreased phagocytosis. Another group showed that similarly obtained alveolar macrophages had increased levels of inducible nitric oxide synthase (iNOS), a traditional marker of M1 macrophage polarization (42). In addition to PGE2, chronic inflammation is also thought affect macrophage function so as to reduce phagocytic capability, perhaps because of inflammatory cytokines produced by alveolar macrophages or other myeloid cells. One group found IL-6 and IL-1 to be elevated in patients with NSCLC relative to patients with benign lung disease (43) while another showed elevated levels of TNF- α and IL-6, but not IL-1, in patients with NSCLC (44), suggesting that tumors may influence both TAMs at the tumor site and alveolar macrophages throughout the lung. Notably, IL-1, IL-6, and TNF- α

tend to be associated with M1 macrophages. Could these macrophages be contributing to tumor growth, as noted in the aforementioned LLC and TLR2 preclinical study (15)? The ability of tumors to influence macrophage function may be limited spatially, as suggested by one study showing that alveolar macrophages in a non-cancerous lobe did not secrete as much TNF- α as did macrophages from a lobe containing cancer (45). Another study of bronchoalveolar lavage samples obtained well away from the affected region still demonstrated impaired phagocytosis (41). An additional study showed that macrophages from the pleural cavity and peripheral blood monocytes in patients with stage I-III lung cancer retained their phagocytic ability while producing the aforementioned pro-inflammatory cytokines (46). These studies suggest that these M1-like macrophages may not have antitumor functions, because they have lost some ability for phagocytosis and tend to create a pro-inflammatory environment. Although these cytokines can be important for antitumor effects, evidence exists to suggest that TNF- α (47,48), IL-6 (49), and IL-1 (50,51) may also participate in cancer progression.

Tumor-associated neutrophils have been less well studied with regard to lung cancer outcomes. Conflicting results have been published, with one study showing worse overall survival based on CD10 expression (52) and one showing no difference between CD10+ and CD10- tumors (53). However, in the former study, the authors compared high CD10-expressing tumors with low CD10-expressing tumors, whereas the latter study compared only CD10+ and CD10- tumors. Comparisons based on high, low, or no expression might show clearer correlations with overall survival, as suggested by studies that compared neutrophil-to-lymphocyte ratios in the blood of NSCLC patients with outcome. A meta-analysis of 14 studies comparing this ratio with outcome confirmed that a higher neutrophil-to-lymphocyte ratio correlated with worse survival in patients with lung cancer (54). Interestingly, one study found that elevated neutrophil counts alone was enough to predict poor survival (55), implying that systemic inflammation may be a risk factor in patients with cancer. Lastly, isolated neutrophils from early-stage lung tumors seem to exhibit immune-stimulatory properties; in one study, neutrophils from resected tumors that were cultured with T cells were able to drive T cell proliferation via the co-stimulatory molecules 4-1BBL, OX40L, and CD86 (56).

Elevated blood levels of MDSCs may correlate also with poorer survival. One group profiled MDSCs in blood samples of NSCLC patients and found that higher levels of

MDSCs, and lower levels of DCs and monocytes, correlated with worse survival (57). Another similar study found no correlation between MDSC levels and survival, but rather that patients with NSCLC generally had increased levels of MDSC in the blood, which correlated with fewer CD8+ T cells (58), implying that the MDSCs might have more of a systemic role as compared with M2 TAMs, which seemed to be changed only locally.

The presence of tertiary lymphoid structures near tumors (59) has been investigated in patients with lung cancer. The first such study in 2008 reported the presence of these structures only in tumors and not in healthy areas of the lung among patients who had undergone surgical resection (60). These tertiary lymphoid structures were found to contain DCs, and the presence of high levels of DC-Lamp+ DCs (a maturation marker) was associated with improved disease-free survival. Notably, tumors with DC-Lamp levels also had more T cell infiltration, more B cells, and more T-bet+ Th1 (helper) cells. Tertiary lymphoid structures seem to be capable of recruiting T cells through several mechanisms (61), and their presence correlates with higher T cell numbers within both the stroma and tumor (62). DC-Lamp-high tumors have also been linked with higher 5-year overall survival rates (60% *vs.* 40% for DC-lamp low tumors). Another study comparing levels of B cells and DC-Lamp+ DCs in tumors reported a similar trend: tumors that had higher levels of mature DCs tended to have higher numbers of B cells, which correlated with better survival rates (63).

Lymphocytes

The importance of tumor-infiltrating lymphocytes (TILs) has been well-documented in several types of cancer. One large clinical study (956 patients) sought to correlate various immune markers with the probability of recurrence in patients with stage I adenocarcinoma (64). Higher levels of stromal Foxp3 (the transcription factor found in Tregs) and IL-7 receptor correlated with higher probability of recurrence. However, if the high Foxp3 levels were associated with high CD3 levels in the stroma, the outcomes were similar to those for low Foxp3 levels, hinting that T cell infiltration can trump Treg levels in lung cancer. The same study also showed that higher levels of IL-12 receptor beta-2 within the tumor correlated with lower probability of recurrence. A recent meta-analysis with the goal of evaluating subsets of TILs and prognosis in patients with lung cancer noted that high levels of CD3+ and CD8+ T cells correlated with improved survival, but higher stromal

Foxp3 levels may have been detrimental (65).

The influence of B cells on survival is less clear. As noted previously, tertiary lymphoid structures seem to be capable of housing B cells near the tumor, and the presence of B cells has been correlated with improved survival (63), although this finding has not been consistent (66). Another study showed that infiltration of IgG4-expressing plasma cells in stromal areas correlated with high rates of survival (67), a finding that agrees with *in silico* results (23).

Evidence also links NK cells with improved survival. One group using CD56 as a marker for NK cells found that 88% of their evaluated patients had lower CD56 in the stroma, but the 5-year survival rate was higher among the 11% of patients with high CD56 levels (82% *vs.* 56%) after surgery (39). Another group found similar results with NK-cell infiltration (68).

Conclusions from the lung TME

TAMs, neutrophils, MDSCs, and Tregs all have immunosuppressive activity in the lung TME. Macrophage function seems to be altered locally, whereas MDSCs may be affected systemically. In line with other types of cancer, the presence of T cell infiltration in lung tumors, mature DCs, NK cells, and, surprisingly, B cells seems to correlate with favorable prognosis.

Radiation therapy and the immune cell response

Radiation therapy (XRT) modifies immune responses in the TME in contradictory ways. It enhances MHC class I expression, which enables the immune system to react to tumor neoantigens (69). XRT also activates immunogenic cell death via the expression of calreticulin on tumor cell surfaces and the release of ATP and HMGB1 (70,71). XRT can also promote abscopal responses with or without immunotherapy through several mechanisms, including upregulation of various trafficking receptors and CD8+ T cell recruitment (72-75), even though lymphocytes are quite sensitive to radiation and are killed shortly after XRT.

One well-studied effect of XRT is its ability to increase transforming growth factor-beta (TGF- β) levels (76). TGF- β is critical for Treg polarization and could contribute to increased Treg representation after XRT; however, Tregs are also inherently resistant to radiation (77-79). XRT also has several roles in recruiting myeloid cells to the TME (80); XRT recruits MDSCs and macrophages and, depending on the radiation dose, polarizes macrophages to

the M2 phenotype. In one study of the LLC model, CD18 hypomorphic mice responded better to a single 20-Gy fraction of XRT because of reduced recruitment of myeloid cells (81). However, another group found that a higher dose (a single 30-Gy fraction) led to recruitment of mainly CD8+ T cells, and that fractionation (3 Gy ×10 fractions) led to recruitment of MDSCs (75). Indeed, these conflicting results after XRT may help to explain why some patients respond to therapy combining XRT and immunotherapies, especially immune checkpoint blockade, while others do not.

Immune checkpoint inhibitors

Our focus on the lung TME was chosen specifically to illustrate the effects of combined checkpoint inhibitors and XRT at the level of the TME. The first checkpoint inhibitor approved for NSCLC, an antibody to the programmed death 1 (PD1) receptor, inhibits a membrane protein expressed on T cells, B cells, NK cells, activated monocytes, and DCs (82). When bound by its ligand PDL1, which is expressed on the surfaces of tumor cells and myeloid cells, PD1 leads to downregulation of antigen receptor signaling, which inhibits effector cell activity (83). PD1 is also expressed by stimulated T cells, hinting that PD1+ T cells may be both tumor-specific and overstimulated (84). Both CD3+ and CD8+ T cell infiltration correlates with improved survival in NSCLC. PD1 blockade may reinvigorate these T cells, driving the immune response seen in the clinic. Tumors with high PDL1 expression are known to have decreased numbers of TILs (85) and to respond better to anti-PD1 monoclonal antibody than do tumors with low PDL1 levels, suggesting that even if T cells do express PD1, they may not be signaling through PD1 unless the tumor is actively expressing PDL1 (86).

The second common checkpoint inhibitor, anti-cytotoxic T-lymphocyte associated protein 4 (CTLA4), is targeted to a receptor expressed on T cells, extensively so on Tregs. When CTLA4 is bound by CD80 or CD86 on an antigen-presenting cell, it transmits an inhibitory signal to T cells but promotes Treg immunosuppressive functions (87). Because CTLA4 binds to CD80 and CD86 with greater affinity than to the costimulatory receptor CD28, T cell activation leads to increased expression of CTLA4 as a means of negative feedback to prevent autoimmune reactions (88). Recent evidence suggests that the primary mode of action of anti-CTLA4 drugs in mice is not to promote stimulation of effector T cells but to deplete Tregs via antibody-dependent cell-mediated cytotoxicity (89).

Although PD1 targets T cells that have already been activated and CTLA4 may deplete Tregs, it is important to note that other immune cells are present in the lung TME; myeloid cells in particular seem to have large role in immunosuppression.

Preclinical studies of PD1 or CTLA4 + XRT

Few preclinical studies have been done that combine anti-PD1 or anti-CTLA4 and XRT in models of lung cancer. In one such study, combining PD1 blockade with XRT in a mouse model of KRAS-mutant NSCLC yielded significantly improved survival and smaller tumor volumes in comparison with control and monotherapy groups (90). XRT + anti-PD1 was capable of causing regression in the 344SQ (p53 and KRAS mutant) NSCLC line (91), and two of eight mice treated with this modality experienced complete tumor regression and were resistant to tumor rechallenge. The anti-CTLA4 antibody was first reported to increase the antitumor activity of XRT in 2014 (92); combining anti-CD25 with XRT in a lung cancer model led to significant decreases in Tregs both at the irradiated site and distally at nonirradiated sites relative to either therapy given alone (93). One could expect similar results with anti-CTLA4 and XRT for the following reasons: (I) CTLA4 acts to reduce Tregs; (II) Tregs seem to have important roles in the lung TME; (III) and XRT may increase the numbers of Tregs in the lung TME.

Future directions

Applying XRT to multiple sites of disease

Key questions remaining for the use of XRT with immunotherapy are the optimal radiation dose and schedule, tumor location, and extent of tumor to be irradiated. Several of the ongoing trials of XRT plus immunotherapy treat only one metastatic site; however, targeting multiple sites or even all areas of gross disease may be much more likely to improve systemic responses. One advantage of such an approach would be to prompt the release of greater numbers of neoantigens from different sites of metastasis, which would improve the probability of priming more T cells, perhaps translating into improved systemic control. Another challenge to the destruction of cancer via the immune system is low T cell penetration into the tumor; for example “cold” tumors without T cells are much less likely to respond to checkpoint inhibitors. Destroying all sites

of gross disease with XRT would abrogate this problem. Irradiation of all disease sites may not be feasible for some patients, and it could well increase toxicity, especially for colitis from treating abdominal disease. Recent trials have demonstrated improvements in outcome from aggressive ablative therapy for patients with up to 3 sites of metastatic NSCLC (94), and there could be further improvement with the addition of immunotherapy.

Using XRT to increase response rates to adoptive T cell therapy

Adoptive T cell therapy has recently gained attention for its potential as systemic antitumor therapy. Because TILs consist of CD4+ and CD8+ lymphocytes, some TILs directly destroy tumors and others promote stimulation of other immune cells (B cells, macrophages, CD8+ T cells) to promote tumor-cell lysis (95). This may explain why the presence of TILs is a prognostic factor for overall and event-free survival as well as recurrence in melanoma, breast cancer, and ovarian cancer (96-98). Efforts have begun to investigate the infusion of expanded autologous T cells isolated from resected tumors.

Given the ability to isolate, extract, and expand TILs, XRT has taken on new promise for improving distant disease control. Metastatic disease is common in NSCLC, for which the mainstay treatment is chemotherapy. However, chemotherapy is lymphocyte-depleting and (99) cannot penetrate the blood-brain barrier. Replacing chemotherapy with tumor-specific T cells may be a way of resolving this difficult issue, as preclinical studies have shown that T cells can penetrate the blood-brain barrier (100,101). Infusing TILs that have been expanded *ex vivo* with the greater antigen receptor diversity generated from definitive XRT could enhance the penetration of those cells into metastases in the brain and at other sites.

Conclusions

Immunotherapy has profoundly changed the care of lung cancer patients. Maximizing its utility requires a deep understanding of the TME. Although anti-PD1 agents have shown to be effective against NSCLC, additional immune cell populations will need to be targeted to increase response rates. Of all the immune cell populations that have been implicated in NSCLC, immunotherapies targeting TAMs and MDSCs are likely the most critical because XRT recruits these cells to the TME. XRT could also be used to recruit T cells to multiple sites and, with immunotherapy,

could also be useful for enhancing the production of TILs, which could then be harvested for expansion as a more diverse population of tumor-specific T cells. These and other strategies will lead to improved clinical outcomes for patients with NSCLC.

Acknowledgements

The authors are indebted to Christine F. Wogan of MD Anderson's Division of Radiation Oncology for editorial assistance and David M. Aten in MD Anderson's Medical Illustration and Multimedia for graphics assistance.

Funding: This work was supported by an MD Anderson Knowledge Gap award, Doctors Cancer Foundation Grant, The Lung Cancer Research Foundation, Cancer Center Support (Core) Grant CA016672 from the NCI (to The University of Texas MD Anderson Cancer Center), the Mabuchi Research Fund, the family of M. Adnan Hamed, the Susan and Peter Goodwin Foundation, the Orr family, and the VanSteklenburg family.

Footnote

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

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Cite this article as: Schoenhals JE, Seyedin SN, Anderson C, Brooks ED, Li YR, Younes AI, Niknam S, Li A, Barsoumian HB, Cortez MA, Welsh JW. Uncovering the immune tumor microenvironment in non-small cell lung cancer to understand response rates to checkpoint blockade and radiation. *Transl Lung Cancer Res* 2017;6(2):148-158. doi: 10.21037/tlcr.2017.03.06

Clinical experiences of combining immunotherapy and radiation therapy in non-small cell lung cancer: lessons from melanoma

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: A Kalbasi; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Radiation therapy (RT) is an essential component of local control for non-small cell lung cancer (NSCLC), but distant failures dictate the poor prognosis of this disease. Until recently, the possibility of using RT as an immunoadjuvant to stimulate a systemic anti-tumor immune response was not a realistic clinical opportunity. The emergence of immune checkpoint blockade as an effective immunotherapy for NSCLC has opened the door for combinatorial approaches involving RT. In melanoma, the body of preclinical evidence combining radiation and immunotherapy buoyed clinical efforts, from which promising results have begun to emerge. Preclinical work combining radiation and immunotherapy indicate similar findings in NSCLC, and clinical efforts are ongoing. Here, we review the rationale, preclinical evidence, ongoing efforts and anticipated challenges of efforts combining radiation and immunotherapy in NSCLC.

Keywords: Radiation; immunotherapy; checkpoint blockade; non-small cell lung cancer (NSCLC); lung cancer

Submitted Oct 17, 2016. Accepted for publication Mar 14, 2017.

doi: 10.21037/tlcr.2017.03.03

View this article at: <http://dx.doi.org/10.21037/tlcr.2017.03.03>

Introduction

The emergence of immunotherapy as the fourth pillar of cancer therapy, alongside surgery, radiation and chemotherapy, has generated interest in combinatorial strategies to maximize the benefits of anti-tumor immunity. The Food and Drug Administration (FDA) approval of immune checkpoint blockade in the treatment of metastatic non-small cell lung cancer (NSCLC) has specifically ignited efforts toward combinatorial approaches in NSCLC. Radiation therapy (RT) may be well suited as a partner to immunotherapy in NSCLC given its immunoadjuvant properties and its utility across the spectrum of patients with NSCLC. While combinations of RT and immunotherapy in NSCLC are still nascent, there is a body of preclinical literature supporting this approach. Moreover, emerging clinical data in melanoma and other disease sites support

testing combinations of RT and immunotherapy in NSCLC.

The need for greater systemic control in NSCLC

NSCLC is the leading cause of cancer death in the United States with an estimated 158,080 deaths in 2016 (1). RT plays a prominent role in the treatment of NSCLC patients across the spectrum of disease: early stage, locally advanced and metastatic. In the growing population of patients with early stage disease, curative local therapy (surgery or stereotactic body radiotherapy) results in 5-year survival rates below 55% (SEER 2005–2011) and 3-year distant metastasis rates between 20–40% (2). For patients with locally advanced or metastatic disease, outcomes remain poor: 5-year survival rates reach 25% for locally advanced stage IIIA patients (2). Patients with metastatic disease

treated with platinum-doublet therapy have a median survival less than 1 year.

In the absence of better systemic disease control, even the most effective RT will have limited gains. Cytotoxic chemotherapy has had limited efficacy for patients with locally advanced and metastatic NSCLC. Several studies demonstrated a survival benefit to adjuvant chemotherapy after resection of non-metastatic NSCLC (stage II-III) (3-7). Adjuvant chemotherapy does not improve clinical outcomes in stage IA patients. For stage IB patients, CALGB 9633 found no benefit to adjuvant chemotherapy, notwithstanding a posthoc analysis suggesting benefit for patients with tumors >4.0 cm (8). Even in the unplanned subgroup analysis of patients with tumors >4.0 cm, the modest benefit of adjuvant chemotherapy must be weighed against its toxicities.

Other approaches, including angiogenesis inhibitors, have had limited success (9,10). The emergence of next generation sequencing has helped identify patients whose tumors harbor mutations for which targeted therapies exist. With this type of personalized medicine, profound responses are observed. However, this approach is limited to a small subset of patients whose tumors harbor actionable mutations (11).

Thus, additional approaches are needed to combat this devastating disease. Immunotherapeutic approaches are the most promising of the emerging therapies for NSCLC. These approaches were first successful in melanoma, a disease in which the immune activating factor IL-2 emerged as a standard therapy in the 1980s (12). Adoptive cell transfer of tumor infiltrating lymphocytes (TIL), and subsequently T cell receptor engineered lymphocytes, induced profound responses in melanoma in the 1990s and early 2000s. But it was not until 2011, when level I evidence demonstrated the survival benefit of immune checkpoint blockade targeting the immunoregulatory molecule CTLA-4, that immunotherapy attracted the attention of a global audience (13). This was followed closely by clinical trials demonstrating the efficacy of a second class of immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) (14).

In 2015, immune checkpoint inhibitors targeting the PD-1 pathway were approved by the U.S. FDA for treatment of patients with locally advanced or metastatic NSCLC that had progressed on prior therapy. More recently the results of the KEYNOTE-024 trial randomized previously untreated patients with metastatic PD-L1 positive NSCLC to pembrolizumab, a humanized monoclonal antibody

against PD-1, versus standard chemotherapy and showed a significant survival benefit in favor of patients receiving pembrolizumab (15).

Rationale for immunotherapy in NSCLC: the shoe fits

Before the approval of immune checkpoint blockade (anti-PD1 therapy) for metastatic NSCLC, there were hints in studies of the immune microenvironment of these tumors that immunotherapy could be an effective approach. Several studies have examined the association of tumor infiltrating lymphocytes TIL on outcome in patients with NSCLC. The interest in TIL may be largely based on observations of heavy T-cell infiltrates in melanoma, a disease highly responsive to immunotherapy. In melanoma, the rich T-cell infiltrate serves as the basis for TIL therapy, in which TIL are grown *ex vivo* for therapeutic intravenous administration in combination with myeloablative regimens and immune growth factors (e.g., IL-2).

Across numerous studies, the presence of CD8+ T cells within the NSCLC tumor microenvironment was associated with superior clinical outcome, despite heterogeneous clinical populations and quantification methods (16). Even more recently, a study examined the association of TIL with survival in a more homogeneous population of patients with resected NSCLC who were enrolled on clinical trials testing adjuvant chemotherapy. The presence of TIL was associated with improved overall survival in this dataset (17). These data supporting TIL as a prognostic factor lend credence to the potential anti-tumor role of infiltrating T cells in NSCLC, as in melanoma.

In addition to TIL, the burden of somatic mutations in a particular tumor may determine its immunogenicity. Effective immunotherapy is based on the premise that T cells recognize a non-self antigen presented by tumor cells. One hypothesis is that tumors with greater mutational load also have greater neoantigens repertoire, increasing the likelihood of a productive anti-tumor T cell response. Compared to other cancer types, melanoma has the highest burden of somatic mutations, thought to be a result of UV-light exposure (18). Consistent with this hypothesis, melanoma patients with higher mutational load are more likely to derive clinical benefit from anti-CTLA-4 immune checkpoint blockade (19).

The two major subtypes of NSCLC, squamous cell carcinoma and adenocarcinoma, carry the second and third highest mutational burden of all cancer types. This

heavy mutational signature may be related to the effects of tobacco smoking. It is plausible that like melanoma, the greater mutational burden seen in NSCLC results in a higher likelihood of tumor reactive T cells that may mount a productive anti-tumor response under the appropriate stimulus. And in line with findings in melanoma, NSCLC patients with tumors harboring higher mutational load, anti-PD-1 immune checkpoint blockade was more effective (20).

Clinical data for immunotherapy in NSCLC

The FDA approval of pembrolizumab was based on results of an international phase 1 study of pembrolizumab (KEYNOTE-001) that included 495 patients with locally advanced or metastatic NSCLC (including both squamous and non-squamous histology). In these patients there was an overall response rate of 19.4%, including a response rate of 45.2% in the PD-L1 high-expressing population (21). Because of the latter finding, its approval was limited to patients with tumors expressing PD-L1.

Two trials compared an alternate antibody antagonist of PD-1, nivolumab, with docetaxel in the second-line treatment of metastatic squamous or non-squamous lung cancer (CheckMate-017 and CheckMate-057, respectively) (22,23). For both CheckMate-017 and CheckMate-057, 2-year overall survival was higher in the nivolumab arm (23% *vs.* 8% and 29% *vs.* 16%, respectively). Unlike CheckMate-057, there was a statistically significant increase in progression-free survival for patients on CheckMate-017 and responses were not tied to baseline PD-L1 expression. Nivolumab was approved by the FDA in March of 2015 for treatment of advanced squamous cell NSCLC refractory to chemotherapy.

Despite the overwhelming success of immune checkpoint blockade, the majority of patients do not respond. Combination therapies—including those with RT—may circumvent the resistance mechanism and expand the efficacy of immune checkpoint blockade to larger fraction of patients with NSCLC.

Rationale for radiotherapy as an immunoadjuvant

Radiation is classically categorized as a DNA-damaging, cytotoxic therapy. However, in addition, it acts as an immunomodulator. The interest in radiation as an immunomodulator began nearly half a century ago, with the first anecdotal reports of the abscopal effect (24). The abscopal effect is a clinical response in a malignant

lesion other than the target lesion (or a response outside the irradiated field), and was posited to be a result of an immunologic response incited by radiation to the target lesion.

Over the subsequent decades, scattered cases of the abscopal effect were reported, but these were met with healthy skepticism. As immune checkpoint blockade and other immunotherapies began to emerge over the past decade, reports of the abscopal effect became more prominent (25). Concurrently, the body of preclinical evidence on the intersection of radiation and immunity began to grow exponentially. These have been reviewed extensively elsewhere (26-28).

Importantly, the local effects of radiation were noted to be immune dependent in specific mouse models. In a murine model of melanoma, the depletion of CD8+ T cells abrogated the local effects of irradiation (29). Likewise, in a murine model of colon cancer, the local effects of radiotherapy were partially dependent on IFN-alpha receptor and stimulator of interferon genes (STING) signaling (30). In both of these studies, the local anti-tumor effects of radiation could not be uncoupled from the T cell immunity. That radiation can incite a local anti-tumor T cell response supports the possibility that it may incite a systemic anti-tumor T cell response, otherwise known as concomitant immunity (31).

Indeed, studies in an animal model of breast cancer demonstrated that ablative radiation of a local tumor impeded the development of lung metastases in a CD8+ T-cell dependent fashion (32). These results have been corroborated by several studies where local irradiation and systemic immunotherapy led to improved tumor control compared to either therapy alone (32-36).

Several mechanisms have been proposed by which radiation potentiates an anti-tumor T cell response. Radiation can induce the release of danger signals or danger-associated molecular patterns (DAMPs), which serve as the first step in a cascade that leads to activation of antigen presenting cells (APCs)/dendritic cells. Danger signals, such as HMGB1, can bind to toll like receptors on the surface of APCs and potentiate the ability of APCs to activate nearby T cells (37). Thus, indirectly via release of DAMPs or via release of specific chemokines (e.g., GM-CSF), radiation may modulate antigen presentation. Radiation can also lead to increase in the quantity, variety and presentation of antigens from a tumor through activation of proteasome pathways, and augmentation of MHC class I presentation (38,39). Radiation-induced chemokines may

also directly attract APCs or effector CD8⁺ T cells to the tumor microenvironment (40).

Radiation can also have immunosuppressive effects that may counteract the development of systemic anti-tumor immunity. Foremost, radiation can recruit immunosuppressive myeloid cells (e.g., myeloid derived suppressor cells, inflammatory monocytes, or tumor-associated macrophages) that either directly promote tumor outgrowth (41), or contribute to be an immunosuppressive microenvironment in which T cells are dysfunctional (42). Additionally, radiation has been shown in pre-clinical models to upregulate PD-L1 expression in the tumor microenvironment, which can lead to T-cell exhaustion (36). Finally, radiation can lead to accumulation of T-regulatory cells, which serve as obstacles to productive anti-tumor immunity (43).

Whether the dominant effects of radiation promote or disrupt anti-tumor immunity may largely depend on tumor type and context. In tumors with baseline immunogenicity, radiation may be more likely to stimulate productive anti-tumor immunity. On the contrary, immunologically “cold” tumors that lack a neoantigens signature and T cell infiltrate, may predominantly recruit immunosuppressive myeloid cells in response to radiation.

Abscopal response to radiotherapy in NSCLC

The majority of clinical data indicating an immunoadjuvant role for radiation are from patients with melanoma. However, data in NSCLC have also emerged. In 2013, clinicians reported a case of an abscopal response to radiotherapy in a patient with metastatic NSCLC who did not receive systemic therapy. The patient received conventionally fractionated radiation (60 Gy) for a T3N0 left upper lobe primary adenocarcinoma, and SBRT (26 Gy ×1) to a right lower lobe primary adenocarcinoma. Two weeks after treatment the patient was noted to have an FDG avid lesion in the adrenal gland consistent with metastasis, and approximately 2 months after treatment developed an FDG avid humeral lesion, also consistent with metastasis. One year after radiation, even without systemic therapy, these lesions had achieved complete metabolic response. The patient ultimately progressed at a different osseous site (44).

The potential for radiation to initiate a systemic anti-tumor immune response has been used as an argument for the treatment of early stage NSCLC with SBRT, especially in contrast to surgery. In a 2010 retrospective study comparing patients with T1-T2N0 NSCLC who

underwent either wedge resection or SBRT, local and locoregional recurrence rates were lower in patients receiving SBRT (45). However, in the pooled analysis of two randomized trials of surgery versus SBRT in medically operable patients (STARS and ROSEL), while SBRT was as effective as surgery (46), there was no significant difference in the rate of regional recurrence or distant metastasis.

Radiotherapy and immune checkpoint blockade

The ability of radiation to initiate systemic anti-tumor immunity may be amplified in the context of immune checkpoint blockade. In animal models, radiation interacts favorably with immune checkpoint blockade. When combined with dual immune checkpoint blockade in a murine model of melanoma, radiation is associated with T cell receptor diversification, and results in greater control of non-irradiated tumors (47). A concordant phenomenon was seen in the peripheral blood from a cohort of patients with metastatic melanoma treated with immune checkpoint blockade (anti-CTLA-4) and palliative radiotherapy. In this cohort, 17% of patients experienced a response in the non-irradiated lesion, which exceeds the expected response rate for anti-CTLA-4 therapy alone.

In the largest dataset thus far examining the effects of local therapy in combination with immune checkpoint blockade (anti-CTLA-4), 127 metastatic melanoma patients were treated with electrochemotherapy, radiation or selective internal radiation therapy (SIRT). After accounting for measured differences in the treatment groups, patients receiving local therapy had significantly longer overall survival (48).

In NSCLC, there are case reports of abscopal responses to radiotherapy in patients also receiving immune checkpoint blockade. In one case, a patient with metastatic lung adenocarcinoma who had progressed despite multiple systemic therapy regimens, received RT concurrently with anti-CTLA-4 therapy and experienced a clinical response in multiple metastatic lesions (49). While it is possible this response was primarily related to anti-CTLA-4, it should be noted that anti-CTLA-4 therapy alone or in combination with systemic therapy has not resulted in improvements in disease outcomes for patients with NSCLC.

A recently reported phase I study of anti-CTLA-4 therapy with SBRT in patients with non-melanoma solid tumors included eight patients with NSCLC (50). Uniquely in this trial, patients received ablative doses of radiation, with BED of ~100 Gy (assuming alpha/beta =10) to the

lung or liver. One out of eight NSCLC patients experienced either a partial response or prolonged (6 months) stable disease outside of the irradiated field (according to immune related response criteria).

Toxicity considerations

Multiple early phase studies have been conducted examining the safety of combining ablative radiotherapy with immunotherapeutic agents (47,51,52). At the University of Pennsylvania, combination ipilimumab with hypofractionated palliative radiotherapy was tested in a phase I study. Of 21 enrolled patients, there was no grade 4 or higher toxicities. The most common grade 3 toxicity was anemia, which was unlikely to be related to the effects of focal hypofractionated radiotherapy.

For the combination of lung radiation and immune checkpoint blockade, pneumonitis is an overlapping toxicity. Radiation pneumonitis and pneumonitis due to immune checkpoint blockade may have shared mechanisms. The precise mechanism for radiation pneumonitis is unclear, but in addition to innate immune responses driven by monocyte, macrophage and neutrophil infiltration (53,54), T cell driven adaptive immune processes have been implicated (55-57). The mechanism for pneumonitis related to immune checkpoint blockade has not been well studied, but is putatively due to autoreactive T cells.

Anti-PD-1 agents have a better safety profile than anti-CTLA4 agents. The rate of grade 3 toxicity for pembrolizumab in NSCLC in KEYNOTE-001 was <10%, including a 1.8% rate of grade 3 pneumonitis. And in modern SBRT series, the rate of grade 3 radiation pneumonitis is <5% (58).

Thus, given the low independent rates of pneumonitis with each therapy, this combination will likely be safe and tolerable. However, given potential overlapping immune mechanisms of pneumonitis related to each therapy, it is important to carefully characterize the safety and toxicity profile in a prospective study. In the aforementioned phase I study of anti-CTLA-4 therapy with SBRT in patients with non-melanoma solid tumors, which included eight patients with NSCLC, clinical pneumonitis was not observed. A phase I safety study of atezolizumab (anti-PD-L1 antibody) in combination with SBRT in early stage NSCLC is actively recruiting patients (NCT02599454, www.clinicaltrials.gov). Likewise, in the metastatic setting, escalating doses of radiotherapy to the lung will be investigated combination with pembrolizumab to assess safety and toxicity

(NCT02587455).

Ongoing studies

In addition to the phase I study of SBRT combined with anti-PD-L1 in early stage NSCLC, other studies are examining combinations of immunotherapy and radiation or chemoradiation in NSCLC (*Table 1*). Many of the trials are conducted in the metastatic or oligometastatic setting, similar to those described above, wherein patients with NSCLC are included with other histologies and the emphasis is to examine the impact of SBRT on efficacy of immune checkpoint blockade or other immunotherapy. At one institution, investigators are testing FLT3 ligand, which may enhance antigen presentation, administered subcutaneously concurrent with SBRT in patients with metastatic NSCLC refractory to standard therapy (NCT02839265).

In studies of early stage and locally advanced disease, the focus of combination studies is to test the efficacy of immunotherapy when added to standard therapy. This includes immunotherapy other than immune checkpoint blockade, such as cancer vaccines that have been tested in the metastatic setting (e.g., cancer-testis antigens such as NY-ESO-1 and MAGE-A3, as well as telomerase and MUC-1). A phase II study of telomerase peptide vaccination in locally-advanced stage IIIA NSCLC suggested patients developed specific immune responses against the peptide in 80% of patients (59). Another vaccine study in locally advanced patients, this one a phase III randomized study, examined the impact of a vaccine against MUC1 glycoprotein on overall survival. While no overall survival difference was noted, the vaccine was associated with a benefit in a subset of patients who had received prior chemoradiotherapy (60).

Other vaccine studies are ongoing for patients after chemoradiation for locally advanced disease. However, combinations using immune checkpoint blockade have generated the most interest, and several trials are ongoing for locally advanced patients. RTOG will be studying adjuvant nivolumab after definitive chemoradiation for locally advanced NSCLC in a randomized phase III design (NCT02768558). Another institution is testing the use of neoadjuvant pembrolizumab for patients with stage IB, II or IIIA NSCLC in a single arm phase II design (NCT02818920). Durvalumab, an anti-PD-L1 monoclonal antibody, will be tested as a neoadjuvant therapy in combination with chemotherapy in patients with resectable stage IIIA NSCLC

Table 1 Ongoing clinical trials combining radiation and immunotherapy for NSCLC

Institution	Disease	Design	Primary outcome	Immunotherapy	Radiation	Combination timing
UC Davis	Stage I NSCLC	Single arm phase I	Safety	Atezolizumab (anti-PD-L1)	SBRT 50 Gy	Concurrent
Weill Medical College of Cornell Univ.	Stage IB and II NSCLC	Randomized phase II	DFS	Durvalumab (anti-PD-L1)	Randomized to surgery or preop SBRT	Concurrent
RTOG/Multi-Institutional	Stage III NSCLC (unresectable)	Phase III randomized	OS, PFS	Nivolumab (anti-PD1)	Thoracic chemoradiation 60 Gy	Immunotherapy after chemo-radiation
Duke Univ./Multi-Institutional	Stage IB, II or IIIA NSCLC	Single arm phase II	Surgical feasibility	Pembrolizumab	Adjuvant thoracic RT if necessary	Not concurrent
UC Davis	Stage IV or recurrent NSCLC	Single arm phase I	safety	MPDL3280A (anti-PD-L1)	SBRT	Concurrent; induction; or sequential
Royal Marsden Hospital	Metastatic NSCLC	Phase I dose escalation	safety	Pembrolizumab (anti-PD1)	Palliative RT (low-dose, high-dose)	
Albert Einstein College of Medicine	Metastatic NSCLC	Phase 2	PFS	FLT3 ligand (CDX-301) – given subcutaneously	SBRT to lung lesion	Concurrent

NSCLC, non-small cell lung cancer; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival; SBRT, stereotactic body radiotherapy.

(NCT02572843). Patients will also receive adjuvant durvalumab, but only after adjuvant radiotherapy, should it be indicated. While these studies may prove a benefit for the experimental agent, they are unlikely to produce data on the potential synergy and radiotherapy.

Resistance mechanisms/future directions

While optimism is abounding regarding these combinatorial successes, failure of these approaches can and should be anticipated. In melanoma, where immune checkpoint blockade has had startling success, a substantial number of refractory cases remain. Some patients do not respond to therapy, and others respond and then progress. Recent evidence suggests that defects in interferon sensitivity within tumor cells may limit the efficacy of immune checkpoint blockade (61,62). Interferon pathway stimulation is likely an important component of the radiotherapy-induced antitumor response as well (30). Thus, identifying patients with NSCLC that lack sufficient interferon pathway signaling, will allow for better selection of patients for clinical trials of combined radiation and immunotherapy.

Conclusions

Some of the immune effects of radiation can induce or boost systemic anti-tumor immunity, especially in tumor with baseline immunogenicity. By doing so, radiation can complement immunotherapies such as immune checkpoint blockade. This is an especially promising approach in NSCLC because of its shared features with melanoma, the disease where immunotherapy has made the most headway. Like melanoma, NSCLC is characterized by a significant number of somatic mutations and a substantial T cell infiltrate. Given these similarities, it is not surprising that NSCLC is one of a handful of malignancies that, like melanoma, responds to immune checkpoint blockade. With the emerging data in melanoma that radiotherapy may improve clinical response rates and outcomes with immune checkpoint blockade, this approach is equally intriguing in NSCLC. We await results from numerous studies testing this approach in the early stage, locally advanced and metastatic settings.

Acknowledgements

None.

Footnote

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

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Cite this article as: Kalbasi A, Rengan R. Clinical experiences of combining immunotherapy and radiation therapy in non-small cell lung cancer: lessons from melanoma. *Transl Lung Cancer Res* 2017;6(2):169-177. doi: 10.21037/tlcr.2017.03.03

Immunotherapy and radiation therapy for operable early stage and locally advanced non-small cell lung cancer

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Non-small cell lung cancer (NSCLC) is the most common cause of cancer mortality. Although a significant proportion of patients can be cured with surgery, with or without adjuvant or neoadjuvant chemotherapy and radiation, a significant proportion of patients will fail, particularly distantly. Over fifty percent of patients present with stage IV disease. There are multiple forms of immunotherapy available including T-cell transfer, cytokine therapy, and oncolytic viruses. Checkpoint inhibitors have shown tremendous activity in NSCLC and are currently under intense study given promising data on response. Immunotherapy and radiation therapy (RT) both show significant immune editing activity in NSCLC that may allow the innate and adaptive immune system to help control systemic disease by both radiosensitization and a sustained systemic immune response. Multiple clinical trials are underway exploring the role of adjuvant or neoadjuvant immunotherapy in operable NSCLC. A substantial amount of progress is to be made in terms of optimizing radiation dose and fractionation, immunotherapy type and dose, and integrating both to best realize the benefits of immunotherapy and radiation in operable lung cancer.

Keywords: Radiation therapy (RT); immunotherapy; non-small cell lung cancer (NSCLC)

Submitted Nov 08, 2016. Accepted for publication Mar 15, 2017.

doi: 10.21037/tlcr.2017.03.05

View this article at: <http://dx.doi.org/10.21037/tlcr.2017.03.05>

Introduction

Lung cancer is the leading cause of cancer mortality in the United States. About 25% of patients with non-small cell lung cancer (NSCLC) present with early stage disease, which is potentially curable with standard of care lobectomy (1,2). Local control is generally excellent after surgery or radiation. Stereotactic body radiotherapy (SBRT) has become an excellent alternative treatment option in patients with early-stage, node negative disease (3). Local control is about 90% at 3 years. Early data in patients with operable patients treated with SBRT indicate local control is 92%

and 73% at 5 years for T1 and T2 disease, respectively (4).

For patients with node-positive or locally advanced operable disease, conventionally fractionated radiation therapy (RT) can be integrated in several different ways. In resectable locally advanced patients, typically stage IIIA (AJCC v7), primary surgery is performed before or after platinum-based chemotherapy, and post-operative RT is indicated in disease with persistent N2 lymph nodes. Preoperative chemoradiotherapy is an alternative approach to the treatment of resectable N2 disease. Patients with unresectable locally advanced NSCLC are treated with curative intent concurrent or sequential chemoradiation.

However, there is a critical need to develop better therapeutic approaches to treat patients with early and locally advanced stage disease and to integrate systemic therapies that have the capacity to effectively eradicate micrometastatic disease and create a sustained systemic response.

Patients with early stage disease still have high risk of relapse

Although local control is high for patients with operable NSCLC, systemic relapse remains the predominant failure pattern. Even among patients with the earliest clinical stage of lung cancer, 50% will die within 5 years of diagnosis after lobectomy (5). For patients with Stage II and IIIA disease and good performance status, platinum-based chemotherapy is recommended to improve systemic relapse rates.

There exists a subset of early stage patients with identifiable poor prognostic characteristics. This includes patients with a suboptimal gene profile, and a number of variably expressed tumor markers and oncogenes (6,7). In one analysis, survival at 5 years in low risk Stage I patients was nearly 90%, but in high risk patients survival was nearly 40% (8). An example of a risk factor is histologic subtype of lung adenocarcinoma, where certain growth patterns such as solid or micropapillary indicate poorer prognosis (9-11). We and others have previously reported that increased SUVmax on pre-treatment fluorodeoxyglucose-PET (FDG-PET) correlate with poorer local control and survival after treatment with SBRT, consistent with surgical series (12). Similar to operable patients, unfavorable subsets of patients have been identified in inoperable patients that are at high risk for nodal and distant failures. These are based on tumor and treatment-related characteristics such as age, functional status, tumor size, histology, proximity to the hilum, and deliverable radiation dose (13).

The opportunity to combine immunotherapy and radiation

There exists a growing body of evidence that T-cell checkpoint inhibitors have robust and enduring activity in some patients with metastatic lung cancer (14-17). Approximately 20% of patients with previously treated lung cancers have objective response to anti-PD-1 or anti-PD-L1 therapies. The responses may be remarkably durable and the treatment associated with good tolerability. Thus far in patients with lung cancers these studies have

largely been in patients with metastatic disease, but T-cell checkpoint inhibitors in melanomas have been shown to improve relapse free survival compared to placebo (HR 0.75, $P=0.0013$) (18). There is a critical unmet need to translate the potential benefits of T-cell checkpoint inhibitors into the early-stage setting for patients with lung cancers. Additionally, as it is only a subset of patients who appear to benefit from anti-PD-1 or anti-PD-L1 therapies, there is also a need to identify effective combination approaches that can augment the benefit of immunotherapy for patients (19,20).

In this context, the opportunity to combine immunotherapy and RT represents a unique approach toward several key challenges in the treatment of patients with lung cancers: (I) can immunotherapy be integrated with RT to improve systemic relapse in patients with early stage lung cancers treated with surgery? (II) can RT in combination with immunotherapy be performed safely and can a synergistic, appropriately sequenced combination be determined?

An analogy to this potential relationship exists in the role of concurrent chemoradiation. In multiple solid tumors, including NSCLC, head and neck disease, and gynecologic malignancies, combined modality therapy with RT and chemotherapy is more effective than either alone, and even more effective compared to sequential therapy. This results in both increased local and systemic control (21). Combined modality therapy has been extensively studied as modulating tumor-host interactions and may improve treatment beyond simply radiosensitization of tumor cells.

Immunotherapy exists in many forms including adoptive T-cell transfer, oncolytic viruses, and cytokine therapy, among other modalities. Currently, immunotherapy using immune checkpoint inhibitors has offered unprecedented rates of response and has since attracted intense attention. Thus the focus of this review will primarily be on immune checkpoint inhibitors and their combination with RT in operable NSCLC.

The activity of immunotherapy in inoperable and metastatic NSCLC

Over 50% of patients with NSCLC will present with metastatic disease and will be treated with chemotherapy with or without local palliative RT. Approximately 18% of patients will present with Stage IIIB unresectable disease and will go on to have chemoradiation with curative intent (22). In these populations, immunotherapy,

despite representing an already heavily treated and frail population with a guarded prognosis, has yielded significant improvements in overall survival (20).

The activity of pembrolizumab was reported in a Phase 1 study that analyzed both efficacy and safety (20). After treatment with pembrolizumab, the objective response rate was 19.4%, and the median duration of overall survival was 12 months. In patients with PD-L1 expression in at least 50% of tumor cells, the objective response rate was 45.2% and median overall survival was not reached. The recently published study of first-line pembrolizumab showed it was superior to chemotherapy in NSCLC patients without sensitizing EGFR mutations or ALK translocations that express the protein PD-L1 in more than 50% of cells (23).

Multiple other studies have shown activity of these and other immune checkpoint inhibitors in NSCLC, which has led to several receiving FDA approval for use in first-line or progressive disease (Hellman ASCO 2016) (24,25). These data also indicate there likely exist tumor-specific characteristics to guide whom may best respond to these therapies.

Immune editing with radiation and improved local control when combined with immune therapy in solid tumors

After treatment, tumor cell transformation drives activation of the host immune response, with modifications in both the innate and adaptive systems. A growing body of evidence suggests that RT can quantitatively augment the immune system by directly upregulating tumor-associated antigens (TAAs), augment MHC class I surface expression in a dose-responsive manner, and increase T-cell tumor-specific CD8+ T cells (26,27). Some tumors downregulate MHC expression to evade immune detection, but upregulation characteristics after RT exposure may prevent this.

Beyond MHC class I surface expression, RT may also stimulate the immune system via activating dendritic cells and increasing antigen cross-presentation. This also increases FAS surface expression, which, in turn, induces programmed cell death. FAS is a cell surface receptor that leads to programmed cell death. FAS upregulation ultimately increases the density of tumor-infiltrating lymphocytes, and upregulates PD-L1 expression (28,29). RT already is known to generate inflammation, increase antigen presentation, and modify the tumor microenvironment. In multiple patient reports, the stimulatory effect of RT inducing an abscopal effect (even

in the absence of immunotherapy) has been shown using a variety of RT total doses and fractionation schemes (30).

Multiple preclinical studies show that checkpoint blockade augments the immunostimulatory effects of RT to improve local disease control. Demaria *et al.* showed in breast cancer cell lines that anti-CTLA4 therapy sensitized cells to RT (31). This was additionally demonstrated in an orthotopic glioblastoma model when combining anti-CTLA4 with stereotactic radiosurgery (SRS), a highly potent local therapy. SRS plus checkpoint blockade improved overall survival by 50% as a product of improved local control (32). RT has been shown in melanoma to augment the immune environment leading to the abscopal effect after combination RT and immunotherapy using anti-CTLA4 therapy (33,34). Deng *et al.* first showed that RT upregulated PD-L1, and then showed that anti-PD-L1 therapy enhanced the therapeutic efficacy of ionizing RT. This was primarily accomplished through an enhanced cytotoxic T-cell dependent mechanism. This combined approach also reduced the accumulation of tumor-infiltrating suppressor cells (35). Sharabi *et al.* showed that anti-PD1 therapy, when combined with stereotactic RT in mouse models of melanoma or breast cancer, increased T-cell infiltration into tumor and enhanced antigen presentation in draining lymph nodes (36).

Combined therapy leading to abscopal and sustained systemic response

While the above mentioned studies suggest that RT and immunotherapy may work synergistically to improve local control, but the clinically unmet need even in patients with localized disease is to improve systemic control given the high propensity for distant progression. Deng *et al.* in the same study as above showed both an abscopal effect and a sustained anti-tumor effect after combined therapy. Using a TUBO breast cancer model, mice receiving both anti-PD1 therapy and irradiation of a single lesion showed abscopal effect by growth rate reduction of a second unirradiated tumor. After complete tumor eradication, mice were rechallenged with the same tumor and no palpable tumors developed on the dual-treated mice (35). Park *et al.* showed a similar result with melanoma and renal cancer mouse models; however, they further showed that the increased antigenicity was tumor-specific when mice bore both tumors (37).

Postow *et al.* described a patient with metastatic melanoma who was treated with paraspinal SBRT and anti-

CTLA4 therapy and who was later found to have a decrease in non-irradiated splenic and hilar masses (34). Golden *et al.* found a similar effect when a patient with NSCLC was treated with combined therapy. This patient received liver SBRT for a NSCLC metastasis and anti-CTLA4. Not only did the irradiated lesion improve, but there was also significant improvement in nonirradiated disease in the lung, skeleton, and elsewhere in the liver (38).

Multiple other clinical reports show the abscopal effect in patients who have received combined RT and immunotherapy. In one series on the combination of anti-CTLA4 and RT, there was a range of 3–6 months from after treatment until an abscopal effect was reached. A range of 5–47 months was observed from the occurrence of the abscopal effect until further disease progression (39). It is important to note that there was significant heterogeneity in tumor type, site irradiated, and total dose and fractionation of RT. The optimal RT regimen, dose and fractionation to elicit an abscopal effect in combination with immunotherapy remain indeterminate.

Neoadjuvant or adjuvant immunotherapy studies show promise

Several clinical studies have shown activity of various forms of neoadjuvant immunotherapy, including adoptive cell transfer, vaccines, and tumor necrosis factor (TNF) therapies. A study with neoadjuvant chemo-immunotherapy in Stage IIB–IIIB NSCLC patients used cisplatin and gemcitabine, and then randomized patients to concurrent recombinant TNF fused with thymosin- α . Seventy-one percent had response to chemo-immunotherapy, versus 50% to neoadjuvant chemotherapy alone (Lazutin ASCO 2015). In an updated analysis, the chemotherapy alone group showed a decrease in NK cells while the chemo-immunotherapy group did not (Zlatnik ASCO 2016).

Kimura *et al.* performed a randomized study of adjuvant chemo-immunotherapy versus immunotherapy alone in patients with IB–IV NSCLC after thoracotomy. Patients who received non-curative resections were included. Chemotherapy was given in platinum-doublets, and immunotherapy consisted of activated killer T-cells and dendritic cells. There was a remarkable difference in 5-year overall survival after the addition of immunotherapy after surgery (81.4% *vs.* 48.3%, HR 0.229, $P=0.0013$). In addition, there was improvement in recurrence-free survival (40). A meta-analysis of 4 randomized trials consisting of 472 patients showed a significant benefit of adjuvant adoptive

immunotherapy with a 39% relative reduction in risk of death. Two of the 4 studies allowed RT as part of treatment (41).

The Radiation Therapy Oncology Group (RTOG) proposed a Phase II study of adjuvant immunotherapy and RT in patients with completely resected Stage II and IIIA NSCLC (RTOG 9909, ClinicalTrials.gov number: NCT00006470). Patients received surgery and within 7 weeks, began two anti-idiotypic vaccines (one which mimicked CEA, and the other mimicked the human milk fat globule antigen) and 50.4 Gy in 28 fractions of RT. These vaccines are used to mimic TAAs. Proposed accrual was 54 patients; however, only 22 patients were accrued and the study closed without reporting results.

Current clinical studies in operable patients

There are multiple current clinical trials open exploring neoadjuvant and adjuvant immunotherapy in operable NSCLC, with a significant focus on checkpoint inhibitors given promising results in patients with advanced or metastatic disease. There is significant heterogeneity in the type of immunotherapy utilized, and none currently combine with RT (*Table 1*).

Emerging studies combining radiation and immunotherapy for effectiveness and safety

The prospect of combined modality treatment augmenting curative surgical treatment has significant advantages in NSCLC. Although approaches combining surgery, RT, chemotherapy and immunotherapy are emerging, there is already significant interest in understanding the role of adjuvant immunotherapy after definitive concurrent RT and chemotherapy. The PACIFIC trial aimed to accrue 702 patients with locally advanced NSCLC who received platinum-based chemo-RT, and then were enrolled and randomized to adjuvant durvalumab or observation if they had not progressed after initial therapy (ClinicalTrials.gov number: NCT02125461). This study is closed to accrual and results are expected sometime in 2017. RTOG Foundation 3505 study will enroll patients prior to chemo-RT and randomize 660 patients with stage III NSCLC who will receive chemo-RT followed by adjuvant nivolumab for 1 year, or observation. Both studies will analyze overall survival as their primary endpoint (ClinicalTrials.gov number: NCT02768558).

However, there are unexplored risks to combining chemo-RT, immunotherapy, and surgery. Preoperative RT

Table 1 Active clinical trials using immunotherapy in operable non-small cell lung cancer

Identifier (ClinicalTrials.gov)	Sponsor	Stage	Phase	Immune therapy	Arms	Accrual	Endpoint	Status
NCT02572843	Swiss Group for Clinical Cancer Research	IIIA (N2)	II	Neoadjuvant and adjuvant durvalumab	Cisplatin/docetaxel ± neoadjuvant and adjuvant durvalumab	68	Event-free survival	Open
NCT02818920	Duke University	IB, II, IIIA	II	Neoadjuvant and adjuvant pembrolizumab	Single arm	32	Safety	Open, not yet recruiting
NCT02716038	Columbia University	IB–IIIA	II	Neoadjuvant atezolizumab	Single arm; combined with Nab-paclitaxel and carboplatin	30	Efficacy	Open
NCT02259621	Sidney Kimmel Cancer Center; Memorial Sloan Kettering Cancer Center	I–IIIA	II	Neoadjuvant nivolumab	Single arm	20	Safety	Open
NCT02595944	NCI-EA5142	IB–IIIA	III	Adjuvant nivolumab	Postoperative platinum-based chemotherapy as per standard of care, ± PORT ± nivolumab	718	DFS/OS	Open
NCT02273375	Canadian Cancer Trials Group	IB–IIIA	III	Adjuvant durvalumab	Postoperative platinum-based chemotherapy as per standard of care (no RT) ± durvalumab	1,100	Disease-free survival	Open

NCI, National Cancer Institute; RT, radiation therapy; DFS, disease-free survival; OS, overall survival; PORT, postoperative radiation therapy.

may lead to lung fibrosis or lung edema, resulting in difficult surgery or concerns with wound healing (42). Postoperative RT, particularly in those who have had significant lung volume removed may have compromised lung function from pneumonitis or long-term pulmonary fibrosis.

Some potential RT toxicities may be augmented by immunotherapy, or vice versa. Grade 3 or higher pneumonitis may be seen in 2% of patients after treatment with pembrolizumab, and it is unknown the magnitude of synergy with RT and immune checkpoint modulators on pneumonitis (20). Published data on RT and immunotherapy in other disease sites suggests no significant increase in the risk of toxicity. This includes no significant increased toxicity of immunotherapy when combined with brain SRS or with pelvic RT (43–45).

Our group has shown that combining thoracic RT and immunotherapy is generally safe and yields acceptable toxicities within the range of treatment with thoracic RT alone. The most often encountered toxicities included fatigue, infection, dermatitis, and rash. Pneumonitis, primarily Grade 1 and 2, occurs in approximately 7% of patients. There were no differences in toxicity when comparing patients who received immunotherapy

concurrently or sequential with RT (46).

Challenges to this approach

There is tremendous potential benefit to combining RT and immunotherapy with surgery. Given that the bulk of patients fail distantly, improving systemic relapse rates is of critical importance. However, there are significant emerging challenges in this approach.

First, we must determine which patients are most likely to benefit from this combined modality treatment by (I) identifying patients likely to fail and (II) identifying patients who will respond to RT and immunotherapy. Previous data shows that patients with high pre-SBRT SUV_{max} or adenocarcinoma subtype (e.g., micropapillary or solid) may be the most likely to fail local therapy, and other clinicopathologic markers such as mutation status may enter into consideration (11,12). In addition, not all patients may respond to RT or immunotherapy. There remains discord in identifying patients who may or may not benefit from immunotherapy and what are the best methods to determine this metric (e.g., CD8 T-cells, total lymphocytes, PD-L1 expression, IL-6 plasma levels, etc.) (47).

For example, studies showing patient's with tumors expressing >50% PD-L1 may be the best responders to certain immunotherapies (20).

After patients are identified, it is unclear what treatment schema to use. There are multiple forms of immunotherapy including multiple checkpoint inhibitors with various targets, vaccines, and adoptive T-cell transfer, among others. There is no consensus in what RT total dose and fractionation to use. Finally, the timing of each of these treatments also lacks clarity. It is unclear whether how best to order therapy whether sequential or concurrent RT and immunotherapy, or if best to use these therapies in the adjuvant versus neoadjuvant setting in relation to surgery. The neoadjuvant setting allows determination of initial tumor response, and possible guidance on post-operative systemic therapy (48).

Once patients are treated with this combined modality approach, it is unclear exactly how to measure treatment response. The most obvious is clinical and imaging evidence of progression-free survival after surgery, RT, and immunotherapy. Even with routinely used imaging modalities responses to immunotherapy can present in unusual fashion such as delayed responses, pseudoprogression etc. Therefore immune-related response criteria were developed and are analyzed in many prospective studies to further evaluate the natural presentation of these immunotherapy responses (49). However, other biomarkers of treatment response should play also be included. These markers may perhaps include measures of immune response and measures of tumor response (e.g., circulating tumor DNA).

There remain a number of concerns in regards to the above with efficacy, timing, type of immunotherapy, dose and location of RT, and measuring response. However, there remains great promise in this approach combining the immune-stimulatory effects of both RT and immunotherapy to decrease systemic relapse rates in patients with otherwise curable disease.

Acknowledgements

Funding: This work is funded by MSK Cancer Center Support Grant/Core Grant (NIH P30CA008748).

Footnote

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

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Cite this article as: Taunk NK, Rimner A, Culligan M, Friedberg JS, Brahmer J, Chaft J. Immunotherapy and radiation therapy for operable early stage and locally advanced non-small cell lung cancer. *Transl Lung Cancer Res* 2017;6(2):178-185. doi: 10.21037/tlcr.2017.03.05

Mini-review of conventional and hypofractionated radiation therapy combined with immunotherapy for non-small cell lung cancer

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: A successful antitumoral response requires immunological activation as well as an antigenic pool capable of stimulating both the innate and the adaptive immune system. Recent advances in immunotherapy have been aimed at boosting the activation status of the innate and adaptive immune system, including cytokine administration, monoclonal antibodies engineered to target high yield elements in oncogenic signaling pathways, cancer vaccines, and checkpoint inhibitors. Herein, we examine the ways that radiation therapy induced cell death provides a pool of stimulus antigen, and draw parallels from the immunobiology of autoimmunity to explore how the immunogenicity of antigen derived from radiation-induced cell death might augment the antitumoral response. We also review basic research into the ability of different radiation dose fractionation schedules to induce an antitumoral response. After a discussion of basic immunotherapeutic principles, we review the published literature in the field of non-small cell lung cancer (NSCLC) and examine the ways that combining radiation and immunotherapy have begun to change the therapeutic terrain. We provide a summary of ongoing clinical trials aimed at combining immunotherapy and radiation therapy in NSCLC while emphasizing the need for identification of biomarkers with predictive power and the assessment of efficacy as a function of fractionation strategy.

Keywords: Radiotherapy; immunotherapy; non-small cell lung cancer (NSCLC); checkpoint inhibition

Submitted Sep 14, 2016. Accepted for publication Feb 20, 2017.

doi: 10.21037/tlcr.2017.03.02

View this article at: <http://dx.doi.org/10.21037/tlcr.2017.03.02>

Immunotherapy and radiotherapy: theoretical and practical synergy

The intuitive appeal of perturbing the immune system to generate an effective anti-tumor response is so profound that the idea emerged contemporaneously with the field of cellular immunology itself. In 1884, Elie Metchnikoff discovered macrophages (1) and Anton Chekov noted a connection between erysipelas and cancer remission (2). Less than a decade later, William Coley was injecting patients with a cocktail of *Streptococcus pyogenes* and *Serratia marcescens* (3-5). Over a century of subsequent empirical

inquiry has uncovered a plethora of interacting signal transduction cascades within a multitude of interacting cell types. We are faced with not only understanding this system, but with purposefully manipulating it for the advancement of human health. Despite formidable immunological complexity, immunotherapy has yielded recent gains in overall survival and disease-free progression in a variety of cancers, most notably: melanoma (6-10), non-small cell lung cancer (NSCLC) (11-14), and renal cell carcinoma (RCC) (15-17). These therapies are designed to work by increasing the activation levels of the immune

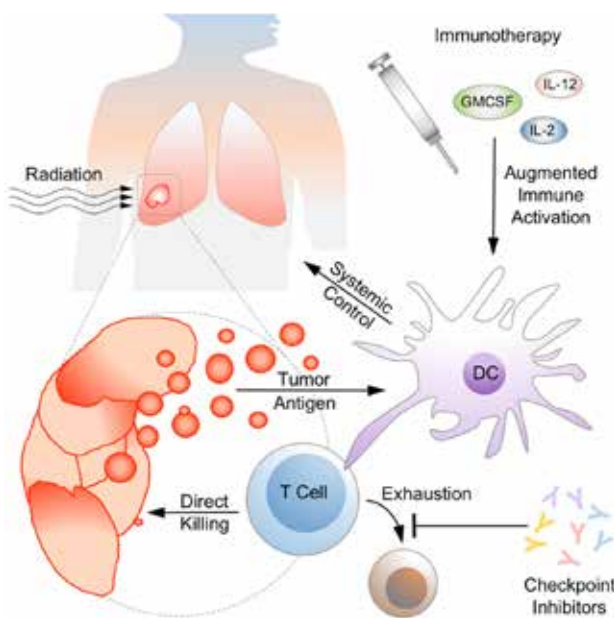


Figure 1 Synergy between radiation therapy and immune therapy in NSCLC. Radiation therapy (top left) releases and alters antigen as targeted tissue dies, influencing immunogenicity in ways we are only beginning to understand. Cellular contents activate the innate immune system, represented here by a dendritic cell (DC), which then leads to an antitumoral response by the adaptive immune system. Immunotherapeutic agents such as cytokines and vaccines (pictured top right), augment immune activation by acting on antigen presenting cells or T cells. Checkpoint inhibitors maintain T-cell activation by blocking inhibitory signaling pathways. Activated T-cells act to improve both systemic and local control. NSCLC, non-small cell lung cancer.

system in response to the antigenic load generated by the tumor in question.

At the most reductive level, harnessing the immune system to attack a tumor consists of two components that are amenable to manipulation: the stimulus and the subsequent response. The word and concept of “immunotherapy” invites a particular focus on the latter, but manipulation of the stimulus (in this case, the antigenic load provided by the tumor) may be equally powerful. The most obvious way to influence the quality or quantity of antigenic load is by inducing preferential killing of tumor cells, either systemically with chemotherapy, or locally with radiation therapy. Increasing the antigenic load and facilitating immune activation with optimal kinetics may achieve a synergistic anti-tumor response, producing an effect on the immune system more definitive and durable than either

approach alone. In this review we will provide a brief overview of the conceptual and empirical underpinnings that make radiotherapy and immunotherapy such promising therapeutic partners before turning our attention specifically to oligometastatic lung cancer and summarizing current experience with the combined approach of radiotherapy and immunotherapy in this particular patient population.

Augmented immunological activation

Like the brain, the immune system generates complex output in response to input that varies in character from the simple to the multiplex. Every fate choice, line of cellular communication, and metabolic activation state becomes a branch point in an intricate effector response that might be modified to produce an improved clinical outcome. Over the past several decades, we have attempted to influence the cytokine milieu, kick-start the innate and adaptive arms of the immune system with vaccines and their adjuvants, and prevent T cell exhaustion with immune checkpoint inhibitors (as depicted in *Figure 1*). A full discussion of the history, breadth, and efficacy of these approaches is beyond the scope of this review, though we will touch on relevant highlights here, with particular attention paid to NSCLC.

Cytokines

Administration of purified cytokines began in the 1980s with IL-2 (18). Dramatic clinical responses in a modest percentage of patients with melanoma (19) and RCC (20) led to FDA approval of IL-2 for the treatment of these diseases, though unfortunately, IL-2—monotherapy did not provide a significant benefit in patients with NSCLC (21). Other gamma-chain cytokines, such as IL-7, IL-15, and IL-21 have theoretical promise in stimulating antitumoral T-cell activation (22), though they have yet to fulfill their bench promise of bedside clinical gains. Cytokines that are major players in innate responses have also been shown to augment the antitumoral response. IL-12 is a particularly attractive immunomodulator due to its ability to activate cytotoxic innate and adaptive responses, but its efficacy in early clinical trials was disappointing and it carried attendant toxicities (23). Interest in IL-12 continues with alternative administration strategies designed to increase intratumoral levels while circumventing systemic exposure (24). GM-CSF has shown promise in murine models of melanoma, and it has consequently been evaluated as a monotherapy and as part of multipronged approaches, with

mixed results (25).

Vaccination

Cancer vaccination is a strategy with attractive theoretical underpinnings, and many ongoing trials are using peptide vaccines, cellular vaccines, or viral-based approaches to stimulate the adaptive immune system to identify and attack tumor cells (26). Of particular relevance to NSCLC was the Phase III MAGRIT trial, which evaluated a peptide vaccine containing MAGE-A3, an antigen expressed in 35% of lung cancers. Unfortunately, vaccination failed to confer any benefit to overall survival (27). Cellular vaccines, composed of cancer cell lines, are intended to provide a selection of antigen that is broad as well as a more authentic stimulus, which allows for cross-presentation by dendritic cells, though in NSCLC there have yet to be any significant improvements in overall survival (28). A viral-based vaccine designed to stimulate an immune response against the antigen Mucin 1 (MUC1), expressed in NSCLC, has shown an improvement in progression-free survival, but has not yet demonstrated a difference in overall survival, though final results from the phase III trial have not yet been published (29).

Checkpoint inhibitors

The most promising immunotherapeutic interventions have come in the form of checkpoint inhibitors, so called because they remove the biochemical brakes on immunological activation. Two such inhibitory pathways have been targeted in T cells: the signaling cascade initiated by cytotoxic T lymphocyte antigen 4 (CTLA-4), and the signaling cascade initiated by the receptor known as programmed death 1 (PD-1) and its ligand, PD-L1, both of which function in T cells. CTLA-4 was first identified as a homolog to CD28, another member of the Ig superfamily known to be essential to the two-signal model of T cell activation (30). Mice deficient in CTLA-4 had a dramatically proinflammatory phenotype (31) and blockade of this pathway enhanced antitumoral immunity in murine tumor models (32). Two monoclonal antibodies have been developed that serve as CTLA-4 antagonists: ipilimumab and tremelimumab. The first success with CTLA-4 blockade came in a trial of ipilimumab used as a second-line agent in melanoma, which showed an advantage in overall survival (7). The beneficial effects of ipilimumab extended to other cancers, including NSCLC, where a regimen of ipilimumab and paclitaxel increased overall survival when compared with paclitaxel alone (11). As of yet,

tremelimumab has not been approved by the FDA for use in treating any cancer as initial trials in melanoma failed to demonstrate significant survival benefit (33).

PD-1 and PD-L1, a receptor and ligand respectively, control T cell exhaustion, maintain tissue tolerance, and initiate resolution of inflammation (34,35). Mice deficient in PD-1 do not spontaneously develop flagrant autoimmune disease, though they have a predisposition toward developing spontaneous glomerulonephritis on the B6 background and dilated cardiomyopathy on the BALB/c background (36). Two monoclonal antibodies that target PD-1 have been approved by the FDA for NSCLC: nivolumab and pembrolizumab. Nivolumab has been approved for use in second-line NSCLC based on the results of a phase III trial comparing nivolumab to docetaxel which showed a benefit in overall survival (12,13). Pembrolizumab was also found to confer an overall survival benefit in NSCLC patients who failed other therapies and whose tumors expressed PD-L1 (37). Atezolimumab and durvalumab are two of several antibodies under development that target PD-L1 rather than its receptor. Atezolimumab was initially approved by the FDA for its promise in bladder cancer (38), and a recently completed phase II study has demonstrated an increase in overall survival in patients with previously treated NSCLC (39).

Biomarkers

Checkpoint inhibitors have been notable for the durability and magnitude of the clinical responses they effect in certain subpopulations of patients. There is consequently a great deal of interest in identifying biomarkers that, used as screening tools, would signify a higher pre-test probability of response in a given patient. The B7 family of cell surface proteins consists of related ligands for CTLA-4 that are expressed by many different cancers, including NSCLC (40). Perhaps because of the wide variety of B7 family members that are expressed on host antigen presenting cells at baseline, no surface marker has yet been identified capable of predicting response to ipilimumab (41).

Significantly more progress has been made in predicting responses to PD-1 blockade. PD-1 transduces an inhibitory signal after binding its ligand; therefore, patients with tumors expressing PD-L1 would potentially be good candidates for therapy with nivolumab, pembrolizumab, atezolimumab and durvalumab. PD-L2, which leads to inhibitory signaling through PD-1 (42), is also expressed by tumor cells. Tumoral overexpression of PD-L2 may

render these cancers particularly sensitive to nivolumab and pembrolizumab, while anti-PD-L1 antibodies might fail to provide significant clinical benefit. PD-L1 and PD-L2 status have been determined as part of several trials, and some data is beginning to emerge on the utility of these two molecules as predictive markers. A trial evaluating the use of PD-1 blockade in NSCLC demonstrated that patients with PD-L1 expressing tumors responded to treatment while those without PD-L1 expressing tumors did not (43).

The picture has been complicated by subsequent studies, which have revealed a subset of PD-1 negative tumors that respond to PD-1 blockade (44). Alternative predictive strategies are therefore needed. Venturing beyond surface markers, genetic analysis of the mutational burden in tumors from patients with NSCLC has demonstrated that a high mutational load predicts a positive response to PD-1 blockade (45). Immunohistological characteristics of pre-treatment tumors in patients with melanoma have demonstrated that a preponderance of CD8+, PD-1+ T cells near or within the tumor correlates with robust T cell infiltration and response to anti-PD-1 therapy (46).

Augmented antigenic immunogenicity

When it comes to tumor cells, the manner of death may be as important as death itself when immunological activation is on the line. Recent insights into cellular death pathways have transformed the idea of a binary live/dead fate into interacting signal cascades influenced by cell intrinsic and extrinsic factors. The baseline burden of dying cells is estimated to be on the order of billions of events per day (47,48), and any defect in clearance of this material—whether from deficiencies in complement (49), mutations in Fcγ receptors (50), disruption of phagocytosis (51,52), inability to break down DNA (53)—leads to autoimmunity. Insights into aberrant immune activation and the pathogenesis of autoimmune disease are directly responsible for the development of checkpoint inhibitors. The potential synergy between antigen load and immunological activation is illustrated in *Figure 1*. Proinflammatory cell death triggers the innate immune system to stimulate an adaptive antitumoral response while checkpoint inhibitors sustain that activation by preventing T cell exhaustion.

Forms of cell death and their relative immunogenicity

Here we will describe three forms of cell death in the order of putative increasing immunogenicity: apoptosis, necrosis/

necroptosis, and pyroptosis. Apoptosis is an intrinsically or extrinsically mediated proteolytic cascade that transforms a dying cell into consumable packets that fall away like so many leaves. Dendritic cells take up the debris and present it to T cells. In the absence of costimulatory innate signals, this process promotes and maintains peripheral tolerance (54,55). The canonical contrast to apoptosis is necrosis, a disaster of cytoplasmic swelling, plasma membrane rupture, and organelle degradation that was originally thought to proceed in the absence of intracellular signaling (56). While there is little ambiguity in the fatal mechanical disruption, if necrotic death takes place over the course of hours, there seems to be some room for cellular preparation for the inevitable in the form of a signaling cascade dependent on RIP kinases that is known as necroptosis (57). Pyroptosis is a form of proinflammatory cell death in which pores in the plasma membrane, created by the activity of caspase-1, achieve membrane lysis in seconds and allow undegraded DNA and bioactive cytoplasmic enzymes to spill into the extracellular space (58). This form of cell death has been described in macrophages and other professional phagocytic cells. Our understanding of cellular death pathways is far from complete, and it is worth noting that a binary conceptualization—immunogenic or not—is unlikely to reflect *in vivo* reality. Immunogenic potential of tumor antigen is perhaps better described as a spectrum determined by the load, kinetics, and manner of cellular death. As we move away from morphology-based descriptions and toward biochemical characterization of cellular demise, the hope is that our ability to predict the relative immunogenicity of tumor antigen liberated by chemotherapy and radiation therapy will improve.

Immunological impacts of chemotherapy

Chemotherapy preferentially affects rapidly dividing cells by inducing death or cell cycle arrest. While this is an effective strategy for killing tumor cells, it hampers the ability of the adaptive immune system to mount an effective response against tumor antigen. In the broadest terms, impaired proliferation in the presence of chemotherapy leads to subpar clonal selection, in turn blunting the specificity of the antitumoral response. Furthermore, the cytotoxic action of chemotherapeutic agents has been primarily characterized as apoptotic by *in vitro* studies, which (given the caveats mentioned above) is primarily a tolerogenic form of cell death (59). The picture rapidly complicates when individual agents or classes of agents are considered,

with different drugs interacting to influence the immune system in unexpected ways. As a case in point, imatinib, famous for its specificity, has been shown to activate NK cells to produce IFN- γ in a manner that is independent of mutation status in KIT or PDGFRA when studied in a population of patients with GIST tumors. In these patients, IFN- γ levels correlated with prognosis, suggesting that imatinib-mediated activation of NK cells may be playing a clinically meaningful role (60,61).

Radiation therapy as an immunomodulator

As our understanding of cellular death pathways deepens, we will gain additional tools to assess the role these forms of cell death may play in the tissue response to radiation *in vivo*. The ability of ionizing radiation to induce apoptosis via the creation of double strand breaks has been studied the most, and is reviewed elsewhere (62). We are only beginning to explore the roles that necroptosis, and pyroptosis may play. Necroptosis has been demonstrated to occur in an anaplastic thyroid cell line exposed to radiation *in vitro* (63), but the extent to which this occurs *in vivo* is as yet unknown. Pyroptosis occurs in macrophages in response to multiple signals, including adenosine triphosphate (ATP) (64), which has been demonstrated to be released from cells exposed to ionizing radiation (65). Though it continues to be difficult to study cellular death pathways within the context of a living host, one might predict that if radiation-induced cell death *in vivo* is capable of providing a stimulatory signal to the immune system one might see anti-tumor effects that occur outside the radiation field. Such an “abscopal”, or “away from the target”, effect was first described in 1953 (66). In recent years there have been a small number of patients who, after receiving an immunotherapeutic agent followed by radiation therapy, have had responses outside the radiation field (67-69). The “abscopal effect” is a putative combination of augmented immunological activation with augmented availability of antigen, which gives it a satisfying theoretical appeal. There is little wonder it has so captured the excitement and attention of the oncology community, with the hope that predictable, reproducible, and durable responses in at least a subset of patients might be achieved.

Immunological correlates of fractionation strategies

In a murine model of melanoma it has been demonstrated that both single fraction and multi-fraction regimens

increase the number of tumor-infiltrating lymphocytes that synthesized IFN- γ and lysed tumor cells (70). A subsequent series of experiments in a murine model of breast cancer assessed the ability of fractionated versus single-dose radiotherapy to activate CD8 T cells and elicit an anti-tumor response outside the radiation field found that a fractionated strategy was superior to a single dose. The fractionation regimen consisted of either 8 Gy \times 3 fractions or 6 Gy \times 5 fractions, both of which would be comparable to a hypofractionated, or stereotactic body radiation therapy (SBRT) regimen (71). A second study that compared an ablative to a conventionally fractionated regimen in a murine model of melanoma demonstrated that a hypofractionated regimen was superior to a conventional regimen in its ability to activate CD8 T cells and trigger the reduction or destruction of distant metastases (72). These findings were supported by a study assessing tumor control in a murine melanoma model as a function of dose and fractionation. The most effective strategy was a hypofractionated regimen. The less robust response in the conventionally fractionated regimen was associated with an increase in regulatory T cells (73). It is tempting to hypothesize that cell death induced by conventional fractionation may be more tolerogenic than death via hypofractionation, but ambiguity remains. A murine model examining tumor-associated macrophages exposed to radiation therapy found that high dose radiation caused impaired T-cell recruitment while low dose radiation led to effective T cell recruitment and tumoral killing (74). A follow-up study demonstrated that low-dose irradiation converted tumor-associated macrophages back to the M1 phenotype, which are better able to coordinate antitumoral T cell responses (75).

Immunotherapy and radiation in oligometastatic and oligoprogressive NSCLC

Initial clinical experiences in the metastatic setting

Given that checkpoint inhibitors have yielded promising results in NSCLC, there has been a great deal of interest in combining radiation therapy and immunotherapy in these patients. A case report documenting an abscopal effect in a patient with metastatic NSCLC who was receiving ipilimumab demonstrated a post-treatment immunological response in the form of infiltrating CD8 T cells within an affected supraclavicular node when compared to an adjacent pre-treatment node removed from the same

Table 1 Ongoing trials combining immunotherapy with radiation in NSCLC

NCT#	Phase	Description
Metastatic disease		
NCT02318771	I	Use of anti-PD-1 + RT in patients with metastatic or recurrent solid tumor
NCT02303990	I	RADVAX: use of pembrolizumab + hypofractionated RT in metastatic melanoma or NSCLC
NCT02400814	I	Use of MPDL3280A (anti-PD-1) with stereotactic ablative radiotherapy in patients with stage IV NSCLC
NCT02444741	I/II	Use of dose escalated ipilimumab and SBRT in patients with metastatic solid tumors
NCT02221739	II	Use of ipilimumab and RT in patients with metastatic NSCLC
NCT02831933	II	ENSIGN: use of SBRT and gene therapy prior to nivolumab in patients with metastatic NSCLC
NCT02658097	II	Use of pembrolizumab following SBRT in patients with previously treated stage IV NSCLC
NCT02492568	II	Use of pembrolizumab following SBRT in patients with previously treated stage IV NSCLC
NCT02407171	II	Use of anti-PD1 MK-3475 (pembrolizumab) and stereotactic body radiotherapy in patients with metastatic melanoma or NSCLC
Oligometastatic/oligoprogressive disease		
NCT02621398	I	Use of pembrolizumab with chemoradiation in stage II/III NSCLC
NCT00828009	II	Use of bevacizumab and BLP25 vaccine in patients with stage III NSCLC who have received chemoradiation
NCT02434081	II	NiCOLAS: use of nivolumab consolidation after standard first line chemoradiation in locally advanced NSCLC
NCT02125461	III	PACIFIC: use of anti-PD1 MEDI4736 (AstraZeneca) following chemoradiation in patients with unresectable stage III NSCLC
NCT02768558	III	RTOG 3505: use of chemoradiation with adjuvant nivolumab in patients with locally advanced NSCLC

NSCLC, non-small cell lung cancer; PD-1, programmed death 1; SBRT, stereotactic body radiation therapy.

site. To date there have been no prospective studies combining checkpoint inhibition with radiation therapy for lung cancer. A proof-of-principle trial assessing local radiotherapy in conjunction with the cytokine GM-CSF enrolled 41 patients with metastatic solid tumors, which included 18 patients with NSCLC. An abscopal response was defined as: “a decrease in the longest diameter of at least 30% in any measurable non-irradiation lesion from baseline”. In patients with multiple tumors outside the radiation field, the best response was reported. According to these criteria, abscopal responses occurred in four patients with NSCLC (68). Further studies are being conducted using a combined approach of radiotherapy and immunotherapy in the metastatic setting, and in coming years we should have an improved idea of the magnitude of benefit a combined approach may provide. Ongoing trials that combine immunotherapy with RT in metastatic NSCLC; these are listed in *Table 1*. The results of a phase Ib trial combining NHS-IL2 with radiotherapy in NSCLC patients who had received first-line palliative

chemotherapy have recently been published. Thirteen patients were treated with varying doses of NHS-IL2. Though the trial was not designed to test efficacy, two patients achieved long-term survival, defined as >4 years from first chemotherapy (76).

Immunotherapy in the oligometastatic and oligoprogressive settings

While the abscopal effect has inspired intense interest, there are other ways in which immunotherapy and radiation might advantageously be combined. Oligometastatic disease has no consensus definition but is understood to represent a low disease burden, with limited spread. Immunotherapy, if used in this setting, may enhance the efficacy of local control by stimulating the immune system to respond more robustly within the radiation field, perhaps significantly prolonging survival and improving quality of life by giving a boost to the “three Es” of immunoediting—elimination, equilibrium, and escape. In the oligometastatic setting,

the first line use of radiation and immunotherapy may increase the magnitude of the initial round of tumoral elimination and prolong and enhance the amount of time the immune system is able to keep growth in check during the equilibrium phase. The combination of radiation and immunotherapy may also have a role in the oligoprogressive state where most sites of disease are responding to therapy but one or two continue to progress. It may be that the combined approach of immunotherapy and radiation directed at the progressing site is capable of preventing or slowing disease escape.

Ongoing trials and future efforts

Subgroup analyses of large trials have indicated a potential synergy between immunotherapy and select groups of patients who had received radiation therapy. In particular, the START trial, which examined the MUC1 liposomal vaccine, showed no significant difference between vaccine versus placebo, but a subgroup of patients who received concurrent radiation therapy did show a statistically significant benefit (77). Perhaps most promising are the trials combining checkpoint inhibitors with radiation therapy. The Phase III double-blinded PACIFIC trial is evaluating maintenance therapy with an anti-PD-1 agent MEDI4736 versus placebo in patients with stage III NSCLC (NCT02125461). We have provided a list of other ongoing trials in *Table 1*. Further inquiries into the safety and efficacy of combined immunotherapy and radiation therapy in NSCLC are needed, but based on the immunological principles and data reviewed above, there may be certain trajectories that are more fruitful than others. As future trials unfold, the following approaches may be of particularly high yield: (I) prospective investigation into combination therapy should include a gross evaluation of basic immunologic competence, including a quantitative assessment of circulating cellular compartments in the peripheral blood with a particular focus on the CD4 and CD8 T cell compartments, as the ability to mount an effective immune response may be at least correlative if not causative in the efficacy of any immunomodulatory agent; (II) investigation into the biomarkers PD-L1 and PD-L2 should continue, with tumoral expression of these ligands determined for patients receiving anti-PD-1 therapy; (III) given the lack of clarity regarding the immunological benefits of conventional versus hypofractionation, these two strategies should be prospectively compared in the presence

of immunomodulatory agents.

Concluding remarks

The potential synergy of immunotherapy and radiation therapy has begun to blur the boundaries between systemic and local control. As synthesized in *Figure 1*, radiation releases and alters antigen as targeted tissue dies, influencing immunogenicity in ways we are only beginning to characterize, comprehend, and predict. The innate and adaptive immune systems work together to mount responses against tumor cells, aided by immunotherapeutic agents that provide stimulatory signals or circumvent checkpoints that prevent sustained T cell activation. Activated T cells act systemically, but also may play a potentially important role in augmenting radiation-induced local control in the oligometastatic or oligoprogressive setting. The confluence of basic science advances in immunology, radiobiology, and oncology have made this a particularly promising time for translational research. Anton Chekhov, one of the earliest physicians to point out the connection between infection and spontaneous cancer remission, said also: “If you say in the first chapter that there is a rifle hanging on the wall, in the second or third chapter it absolutely must go off.” This dictum is known as “Chekhov’s Gun,” and is meant to be a tool of narrative fiction. But if immunotherapy is that rifle, we have been looking at it for a long time.

Acknowledgements

The authors would like to thank Noah Capurso M. D. for assistance in editing the manuscript.

Footnote

Conflicts of Interest: RH Decker receives research support from Merck & Co., Inc. AM Campbell has no conflicts of interest to declare.

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Cite this article as: Campbell AM, Decker RH. Mini-review of conventional and hypofractionated radiation therapy combined with immunotherapy for non-small cell lung cancer. *Transl Lung Cancer Res* 2017;6(2):220-229. doi: 10.21037/tlcr.2017.03.02

Non-small cell lung cancer (NSCLC) and central nervous system (CNS) metastases: role of tyrosine kinase inhibitors (TKIs) and evidence in favor or against their use with concurrent cranial radiotherapy

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Abstract: Central nervous system (CNS) metastases, including brain metastases (BM) and leptomeningeal metastases (LM) represent a frequent complication of non-small cell lung cancer (NSCLC). Patients with BM comprise a heterogeneous group, with a median survival that ranges from 3 to 14 months. However, in the majority of patients, the occurrence of CNS metastases is usually accompanied by severe morbidity and substantial deterioration in quality of life. Local therapies, such as whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) or surgical resection, either alone or as part of a multimodality treatment are available treatment strategies for BM and the choice of therapy varies depending on patient group and prognosis. Meanwhile, introduction of tyrosine kinase inhibitors (TKIs) in clinical practice has led to individualization of therapy based upon the presence of the exact abnormality, resulting in a major therapeutic improvement in patients with NSCLC who harbor epidermal growth factor receptor (EGFR) activating mutations or anaplastic lymphoma kinase (ALK) gene rearrangements, respectively. Based on their clinical activity in systemic disease, such molecular agents could offer the promise of improved BM control without substantial toxicity; however, their role in combination with radiotherapy is controversial. In this review, we discuss the controversy regarding the use of TKIs in combination with radiotherapy and illustrate future perspectives in the treatment of BM in NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); central nervous system metastases (CNS metastases); tyrosine kinase inhibitors (TKIs); concurrent radiotherapy

Submitted Aug 14, 2016. Accepted for publication Oct 08, 2016.

doi: 10.21037/tlcr.2016.12.06

View this article at: <http://dx.doi.org/10.21037/tlcr.2016.12.06>

Introduction

Non-small cell lung cancer (NSCLC), which accounts for 84% of lung cancer cases in the US, is one of the major causes of cancer-related deaths worldwide (1). Central nervous system (CNS) metastases, including brain metastases (BM) and leptomeningeal metastases (LM) represent a frequent complication; it has been postulated

that approximately 40% and 5% of NSCLC patients will develop BM and LM respectively during the course of the disease (2). Patients with BM comprise a heterogeneous group, with a median survival that ranges from 3 to 14 months (3). However, in the majority of patients, the occurrence of CNS metastases is usually accompanied by severe morbidity and decrease in quality of life.

Through the years, advances in evaluation of BM, such as the development of the Diagnosis-Specific Graded Prognostic Assessment (GPA) score enabled quantification of prognosis and assessment of patient survival (4). Local therapies, such as whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) or surgical resection, either alone or as part of multimodality treatment are available treatment strategies for BM and the choice of therapy varies depending on patient group and prognosis. On the other hand, the role of systemic therapy in the treatment of patients with BM is less well-defined. Recent studies assessing the efficacy of chemotherapeutic agents, such as temozolomide, in combination with radiotherapy in patients with NSCLC and BM have failed to demonstrate any benefit compared to radiotherapy alone, possibly as a result of low blood brain barrier (BBB) penetration (5,6). However, several prospective trials in NSCLC patients with asymptomatic BM have shown substantial activity of first line chemotherapy for BM, with intracranial response rates (RR) comparable to systemic RR, warranting further research on the role of chemotherapy in CNS disease from NSCLC (7-12).

Most recently, an improved understanding of the molecular pathways that drive malignancy in NSCLC triggered the development of agents that act against specific molecular targets in cancer cells, such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Introduction of tyrosine kinase inhibitors (TKIs) in clinical practice has led to individualization of therapy based upon the presence of the exact abnormality, resulting in a major therapeutic improvement in patients with NSCLC who harbor EGFR or ALK activating mutations. Based on their clinical activity in systemic disease, such molecular agents could offer the promise of improved BM control without substantial toxicity; however, their role in combination with radiotherapy is controversial.

In this review, we will discuss the controversy regarding the use of TKIs in combination with radiotherapy and illustrate future perspectives in the treatment of BM in NSCLC.

CNS metastases in NSCLC: current clinical practice

CNS metastases are present at initial diagnosis in approximately 10–20% of patients with NSCLC. Furthermore, it has been estimated that they develop as site of first recurrence following successful locoregional

treatment for non-metastasized locally advanced NSCLC in approximately 18% of NSCLC patients (13). Traditionally, systemic therapies have a limited role in the treatment of CNS metastases, due to presence of a BBB that prevents systemic drugs from reaching brain parenchyma. The BBB is formed by brain endothelial cells connected by tight junctions with high electrical resistivity and acts as a selective barrier between the systemic circulation and cerebrospinal fluid (CSF) (14). BBB is surrounded by a basement membrane covered by podocytes and astrocytes. It permits the passage of lipid-soluble molecules by passive diffusion, in addition to molecules essential for neural function. Selective chemotherapeutic drugs that are able to achieve good BBB penetration are those that are not substrates of efflux transporters, such as P-glycoprotein, which is high expressed by the BBB and carries the majority of drugs outside the intracranial region (15). Nevertheless, the integrity of BBB is usually disrupted following the occurrence of BM at later stages, albeit permeability is inhomogeneous (16). More specifically, when BM reach a size more than 5 mm, the BBB is disrupted, as demonstrated by enhancement upon intravenous contrast medium injection during imaging techniques (12). In addition, WBRT commonly disrupts the BBB. The disruption of the BBB might explain the activity of first line chemotherapy in NSCLC BM (12). However, BM is frequently the site of relapse after curative treatment in NSCLC; this indicates that chemotherapeutic drugs might not sufficiently cross the BBB.

Initial therapy for symptomatic BM includes the administration of corticosteroids to reduce peri-tumoral edema and anticonvulsant therapies in case of seizures (17). Subsequently, treatment depends on the location, number of BM and prognosis. Patients with a single brain metastasis who are good surgical candidates should be offered surgical resection or SRS, as several studies have shown a survival advantage with the addition of surgery or SRS to WBRT compared to WBRT alone (18-20). Patients with 1–4 cerebral metastases should be treated with SRS with or without WBRT. The combination of SRS and WBRT has been shown to improve intracranial control but not overall survival (OS) in patients with oligo metastatic or oligo progressive disease (21,22). On the other hand, the vast majority of patients are not eligible for invasive strategies due to multiple metastases or poor performance status. WBRT represents the only therapeutic option for these patients; it results in improvement of neurological deficits in approximately 30% of patients (23). However,

in the recent randomized QUARTZ trial, that assessed the efficacy of WBRT compared to best supportive care in patients with BM and NSCLC, no clear survival advantage or improvement in quality of life was shown for patients that were treated with WBRT (24).

There is currently no standard of care for the treatment of LM; this is mainly due to the fact that LM occurs relatively rarely. Consequently, there is a lack of randomized studies; available therapeutic options, such as intravenous or intrathecal chemotherapy and radiation of the brain or affected neuro-axis are somewhat based on the treatment of patients with LM and hematological malignancies. In either case, patients with LM carry a dismal prognosis that ranges from 4 to 22 weeks (25,26).

TKIs and NSCLC-associated BM

EGFR TKIs

EGFR TKIs, such as erlotinib, gefitinib and afatinib are the standard therapy for advanced NSCLC patients with EGFR-activating mutations, having shown superiority in progression free survival (PFS) compared to chemotherapy as first line treatment (27-29). There is relative controversy regarding the change of EGFR mutational status during the metastatic process; several studies suggest a poor correlation (30,31), while others have shown consistency between EGFR mutations found in the primary tumor and corresponding BM (32). At present, there is some retrospective evidence supporting a higher incidence of BM in EGFR mutant tumors (33); however, it is unclear whether there is a difference at initial diagnosis. Most importantly, EGFR mutant tumors are more likely to develop BM during the course of the disease mainly due to longer life expectancy. On the other hand, it has been postulated that approximately 14–17% of patients with EGFR mutant NSCLC present with isolated CNS progression after front line treatment with EGFR TKIs (34-37). However, others have demonstrated a lower incidence of BM in the same population (38). In a retrospective report by Heon *et al.*, patients with EGFR mutant NSCLC treated with front line erlotinib and gefitinib had a lower rate of CNS progression compared with patients treated with chemotherapy [21% *vs.* 32% at 1 year, HR =0.56; 95% confidence interval (CI), 0.34–0.94] (39).

In contrast to cytotoxic agents, EGFR TKIs have been shown to cross the BBB. This might be attributed to their low molecular weight; however, concentration in the

CSF is generally much lower than in blood circulation, which partially hampers their ability to reach the brain parenchyma (40,41). Interestingly, higher concentrations are achieved with erlotinib than gefitinib, suggesting an increased efficacy of erlotinib in treating BM (40).

Several case reports have postulated complete and continuous responses following treatment of BM with gefitinib or erlotinib (42-44). Furthermore, gefitinib has clinical activity as monotherapy in unselected patients with NSCLC and BM after failure of standard therapy (45). In patients with EGFR mutant tumors, retrospective data suggest an overall intracranial response of 89% for gefitinib and 82% for erlotinib (2,14,46). Interestingly, erlotinib has been investigated as monotherapy in the management of BM. Gerber *et al.* retrospectively analyzed data from 222 patients with EGFR mutant tumors and newly diagnosed BM who were treated with either erlotinib, WBRT or SRS. WBRT was associated with better intracranial control, albeit similar OS compared to erlotinib. In this study, the authors underlined the importance of WBRT in achieving local control of BM (47). In another phase II trial, erlotinib was evaluated as second line therapy in NSCLC patients with asymptomatic BM and no extracranial progressive disease following first line platinum-based chemotherapy treatment. The median intracranial PFS was 15.2 months for patients with EGFR positive tumors, albeit only 4.4 months for EGFR unselected patients. It is important to note that a series of phase I/II studies using high dose erlotinib for the treatment of LM in patients with NSCLC has shown both efficacy and tolerability (48,49). On the other hand, second generation TKI afatinib has also shown clinical activity against BM. In a study by Hoffknecht *et al.*, afatinib demonstrated a disease control rate (DCR) of 66% in NSCLC patients with BM pretreated with chemotherapy and first generation TKIs (50).

Finally, third generation irreversible EGFR TKI osimertinib, which has been proven effective against EGFR-mutant tumors with acquired T790M resistance, has shown substantial CNS penetration and remarkable CNS activity both at preclinical and clinical level (phase II data) (51-53). Furthermore, in the recent I BLOOM study that was presented in the 2016 ASCO annual meeting and included 21 patients with LM from NSCLC, osimertinib provided LM disease control in 76% of patients, among which 33% had radiologic improvement (54). The majority of patients were heavily pretreated.

Of note, there is a question whether there is a potential role of prophylactic cranial irradiation (PCI) in patients

with EGFR-mutant tumors that are characterized by a higher incidence of BM. In a recent report, patients with L858R mutations have been found to have a greater risk of developing BM (55). There are no randomized studies addressing this issue. A recent study has shown a potential benefit of PCI in patients with surgically resected stage IIIA-N2 NSCLC and high risk of BM after adjuvant chemotherapy (56); however, this study does not provide data on EGFR mutations.

ALK-TKIs

Rearrangement of ALK is seen in approximately 2–7% of patients with NSCLC and is a therapeutic target in advanced NSCLC. It is not clear whether patients with ALK positive tumors present more frequently with BM at initial diagnosis; however, it has been estimated that 60% of patients develop CNS metastases during treatment with first generation TKI crizotinib (57). Several reports suggest a very low CSF to plasma concentration ratio for crizotinib (58,59). In a retrospective analysis of patients with BM included in the pivotal trials PROFILE 1005 and PROFILE 1007 that led to approval of crizotinib as first and second line treatment in ALK positive NSCLC, crizotinib showed an intracranial RR of 18% in untreated BM and 33% in pretreated BM, compared to 50% overall response rate (ORR) in systemic disease (60). Furthermore, patients with no preexisting CNS disease developed BM in 20% of cases, while progressive disease in the CNS occurred in 71.1% of patients with known BM at baseline. Based on data of poor CNS activity of crizotinib, it is suggested that patients experiencing CNS progression on crizotinib should be offered local CNS therapies whereas the administration of crizotinib should be continued.

Novel ALK-TKIs such as ceritinib and alectinib have shown promising activity against BM. In a recent report, efficacy and safety of ceritinib was assessed in a subset of patients with BM in the phase I ASCEND-1 trial. Among 14 patients with BM, 7 had intracranial response, 4 of which have been previously treated with crizotinib (61). On the other hand, alectinib has been designated by the FDA as breakthrough therapy, following the high RR it demonstrated in the phase I/II trial in crizotinib-naïve ALK positive NSCLC patients (62). Alectinib has a better BBB penetration than crizotinib because it is not expelled by P-glycoprotein from the intracranial environment (57). In a phase II trial conducted in crizotinib-resistant or intolerant patients, 21 patients had BM; alectinib achieved

a 52% RR (63). Furthermore, among for patients who have not received WBRT, CNS control was 100% with alectinib. This trial provides evidence that alectinib is active in BM after failure of crizotinib. However, prospective comparison across ALK-TKIs regarding CNS activity is hampered by lack of CSF pharmacokinetic measurements. The randomized phase III ALEX trial is currently assessing the efficacy of alectinib *vs.* crizotinib as front line treatment in ALK positive NSCLC; its design will allow discriminate between intracranial and extracranial failure. Finally, activity of ALK-TKIs in LM is anecdotal (63,64); results are eagerly expected from ongoing phase III trials ALEX and ASCEND-7, which include patients with LM (NCT02075840, NCT02336451).

TKIs with concurrent radiotherapy

Rationale and clinical data

The management of BM continues to pose a major challenge in oncology and current therapeutic options have modest results in achieving good or long intracranial responses. WBRT is the mainstay of treatment for patients with multiple metastases. According to NCCN guidelines, patients with poor performance status should receive a shorter course of WBRT. EGFR and ALK TKIs have demonstrated good clinical activity in systemic disease and might delay CNS progression in patients with EGFR mutant and ALK positive tumors respectively. However, in patients with driver mutations, whether EGFR-TKIs can enhance or replace cranial irradiation in the initial treatment of BM remains unclear. In a recent meta-analysis, upfront radiation therapy was shown to improve intracranial disease control and survival compared to TKI monotherapy in patients with EGFR mutant tumors (65). In this meta-analysis, a small proportion of patients received a combination of WBRT and EGFR TKI. On the other hand, there is evidence that sequential use of TKIs can delay administration of WBRT in EGFR mutant tumors (66). An intriguing question in clinical practice is whether a TKI could be safely combined with WBRT and in which patient population.

Preclinical data support the combined use of radiotherapy and EGFR inhibitors as a strategy for cancer treatment. In the clinical setting, anti-EGFR monoclonal antibody cetuximab has been suggested as a radiosensitizer, demonstrating improved OS in conjunction with radiation compared to radiation alone in patients with squamous cell carcinoma of the head and neck (67), albeit having failed to show any

benefit in combination with chemoradiation in locally advanced NSCLC (68). On the other hand, EGFR TKIs have shown to potentiate radiotherapy response in human carcinoma cell lines *in vivo* and *in vitro* (69,70). Potential mechanisms of synergism include cell cycle arrest, induction of apoptosis, inhibition of radiation-induced DNA repair mechanisms and increased EGFR expression in radioresistant clones (69-71). In addition, radiotherapy might disrupt the BBB, facilitating passage of drugs into the brain (72).

A dose-escalation phase I trial reported by Lind *et al.* evaluated the tolerability of WBRT with concurrent and maintenance erlotinib in an unselected population of patients with NSCLC and BM (73). Patients in cohort 1 received erlotinib at a dose of 100 mg/d before and during WBRT, whereas in cohort 2, erlotinib was administered at a dose of 150 mg/d before and during WBRT; patients in both subgroups received maintenance erlotinib at a dose of 150 mg/d. Out of 11 patients, no serious treatment related toxicity was observed in cohort 1; however, in cohort 2, one patient developed grade 3 rash, one had grade 3 fatigue and two patients died of interstitial lung disease attributed to erlotinib. No neurotoxicity was reported. Interestingly, only one patient experienced intracranial progression, suggesting a high intracranial disease control (73).

Following the results of the phase I study, a phase II study was conducted in patients with NSCLC and newly diagnosed BM regardless of EGFR status (74). Erlotinib was given at a dose of 150 mg/d one week before and concurrently with WBRT followed by maintenance. ORR was 86% in the whole population and median survival was 11.8 months, significantly longer than historical controls. No neurotoxicity was noted. As expected, median PFS and OS were longer in patients with EGFR mutant tumors [PFS: 12.3 *vs.* 5.2 months and OS: 19.1 *vs.* 9.3 months in EGFR wild type (WT) tumors]. This is in concordance with a recent retrospective study that showed an excellent intracranial control and a median OS of 26 months in patients with EGFR mutant tumors treated with WBRT plus EGFR-TKIs (75).

A phase III trial was subsequently performed by the Radiation Therapy Oncology Group (RTOG) evaluating the addition of temozolomide or erlotinib in combination with WBRT and SRS in patients with 1–3 BM and unselected EGFR status (76). The study closed early due to accrual limitations. Median survival was numerically longer with WBRT + SRS compared to WBRT + SRS and temozolomide, or WBRT + SRS and erlotinib (13.1 *vs.* 6.3 *vs.* 6.1 months respectively) albeit not statistically significant. This deleterious

effect in survival was possibly attributed to increased grade 3 to 5 toxicity in the combination arms, which reached 49% with the addition of erlotinib ($P < 0.001$) (76).

In a subsequent randomized, placebo controlled phase II study, patients were treated with WBRT with or without erlotinib in a population of predominantly EGFR-WT patients (77). In this study, only 37.5% of patients were alive and without neurological progression following WBRT and no advantage in neurological PFS or OS was observed with the addition of erlotinib (PFS and OS HR = 0.95). This is the only study demonstrating an absence of efficacy of erlotinib in combination with WBRT in EGFR WT patients. This was confirmed in a recent meta-analysis presented in the 2015 ASCO meeting; in an unselected population of patients with BM, the addition of EGFR-TKIs to WBRT did not provide significant benefit (78).

Gefitinib has also been evaluated in combination with WBRT in phase II trials. In a phase II study conducted in a Chinese population, gefitinib was administered in combination with WBRT, followed by maintenance therapy (79). The study showed promising results; ORR was 86% and OS was 13 months. Most side effects were grade II (rash, diarrhea) and well tolerated. In another randomized phase II trial, patients with NSCLC and BM were treated with WBRT in combination with either gefitinib or temozolomide (80). Median OS was 6.3 months in the gefitinib-WBRT group compared to 4.9 months in the temozolomide-WBRT group. No significant toxicity was observed. Concomitant use of gefitinib and WBRT is further supported by a retrospective analysis that included Chinese patients with BM who were treated with gefitinib with or without WBRT (81). Patients in the combination group demonstrated a superior intracranial DCR, median time to progression of BM and median OS (71.1%, 10.6 and 23.40 months respectively in the gefitinib-WBRT *vs.* 42.2%, 6.57 and 14.83 months respectively in the gefitinib-only group). Nevertheless, these two studies both involve a Chinese population with known intrinsic sensitivity to gefitinib; it is unclear whether results can be generalized in the European population. Of note, no studies assessing the efficacy of afatinib with WBRT have been performed.

The results of those trials were assessed in two recent meta-analyses, designed to evaluate the efficacy and safety of the use of EGFR TKIs with concurrent intracranial radiotherapy in patients with NSCLC and BM. The first meta-analysis, which included 8 studies, demonstrated a superior ORR (HR = 1.56, $P = 0.0008$) and time to CNS progression (HR = 0.58, $P = 0.03$) in patients treated with

WBRT in combination with an EGFR-TKI (TKI-group) compared with patients treated with WBRT without an EGFR-TKI (non-TKI group) (82). Furthermore, no difference in severe adverse events was shown (HR =1.49, P=0.14). The second meta-analysis that included 15 studies had similar results; radiotherapy plus an EGFR TKI resulted in improved RR and DCR (RR =1.48; 95% CI, 1.12–1.96; P=0.005; and DCR =1.29; 95% CI, 1.02–1.60; P=0.035; respectively) than radiotherapy without an EGFR-TKI (83). Moreover, time to CNS progression and median OS were both prolonged (HR =0.56; 95% CI, 0.33–0.80; P=0.000 and HR =0.58; 95% CI, 0.42–0.74; P=0.000 respectively), albeit with an increased rate of any grade adverse events (RR =1.25; 95% CI, 1.01–1.57; P=0.009), especially rash and dry skin. The results of these meta-analyses should be interpreted with caution, due to heterogeneity of the included studies and different treatment modalities combined.

With regards to ALK-TKIs, there is currently no evidence in favor or against their concomitant use with radiotherapy. However, concurrent use should be applied with caution, as it is possible that concurrent radiotherapy could exacerbate ocular toxicity of crizotinib (84).

Clinical trials of radiotherapy plus TKIs in patients with NSCLC and BM are summarized in *Table 1*.

Expert opinion

The paradigm shift occurring in NSCLC is encapsulated by the management of patients harboring activating mutations. In patients with EGFR mutant or ALK positive tumors, front line treatment with EGFR or ALK inhibitors results in high systemic RRs and a lower risk of CNS progression. However, isolated or predominant CNS progression represents a major issue in patients treated with EGFR or ALK TKIs, regardless of impressive initial response. In an attempt to increase intracerebral efficacy, concurrent use of TKIs and radiotherapy is undoubtedly a tempting approach. Advantages would be the possible synergistic antitumor effect against BM, as suggested in preclinical studies, as well as prevention of disease flare, which refers to accelerated progression of disease and subsequent worsening of symptoms following TKI discontinuation (85).

At present, several clinical studies and meta-analyses have shown superior clinical activity in BM with the combination of WBRT and TKIs. However, there are many limitations that need to be addressed. First, most of the studies have been performed in an unselected population. Second, a

phase III trial has demonstrated unacceptable toxicity of the combination of WBRT, SRS and erlotinib (76). Furthermore, in a recent randomized study, WBRT has been shown to impair cognitive function when added to SRS (86). Preservation of cognitive function is of major importance in these patients considering their younger age. In addition, studies evaluating the efficacy of gefitinib are mainly performed in Asian populations, and it is unknown whether results can be globally generalized.

At this time, concurrent use of TKIs with radiotherapy is not recommended outside of a clinical trial. Interestingly, the data in EGFR mutant patients treated with erlotinib alone (47) prompt the question whether this could be a front-line approach in patients with asymptomatic BM, reserving WBRT for symptomatic cases. However, this should probably not be considered in ALK positive tumors, since patients with BM have been shown to have significantly better survival when treated with radiotherapy compared to patients with ALK WT tumors (87). These patients display prolonged survival and interventions to control intracranial disease is crucial (88). Therefore, radiotherapy should be a part of multimodality treatment somewhere in the course of their disease; it has been also suggested that the role of PCI could be reconsidered (89). In clinical practice, burden of extracranial disease and therefore concerns regarding disease flare might also guide treatment decisions; physicians might select not to discontinue a TKI during WBRT in case of extended extracranial disease.

Ongoing clinical trials are currently evaluating the effectiveness of concomitant use of radiotherapy and TKIs. Among them, ENTER is a phase III trial evaluating the addition of erlotinib to WBRT as front line treatment in patients with multiple BM from NSCLC (NCT01887795). Similarly, another study is assessing concurrent use of erlotinib and IMRT (NCT02556593), with the view to reduce neurotoxicity.

Conclusions

In conclusion, the incidence of BM from all cancers is increasing. Current research is focusing on improving management of BM based on genetic background of malignancies. In NSCLC, agents targeting EGFR and ALK have shown very promising results in systemic disease and delay of CNS progression. However, resistance to these agents commonly manifests as isolated CNS recurrence. In an attempt to improve management of BM, combining WBRT with TKIs is a promising approach. Because all these agents are relatively new, their role

Table 1 Summary of trials of radiotherapy plus TKIs in patients with NSCLC and BM

Author/year	Phase	No of pts	EGFR mutation status	Treatment groups	Control group	Outcomes
Lind <i>et al.</i> , 2009	I	11	NA	Cohort 1: erlotinib 100 mg + WBRT; cohort 2: erlotinib 150 mg + WBRT	–	Grade 3–5 toxicity in cohort 2; high IDCR
Welsh <i>et al.</i> , 2013	II	40	EGFR mutant: 9 of 17 pts tested	Erlotinib 150 mg + WBRT	–	ORR 86%; median OS 11.8 months; median OS 19.1 months in EGFR mutant
Sperduto <i>et al.</i> , 2013	III	126 (closed early)	NA	Arm 2: TMZ + WBRT + SRS; arm 3: erlotinib 150 mg + WBRT + SRS	Arm 1: WBRT + SRS	OS not improved with addition of drugs; no difference in CNS-TTP between the three arms; 49% grade 3-5 toxicity in arm 3
Lee <i>et al.</i> , 2014	II	80	EGFR mutant: 1 out of 35 tested	WBRT + erlotinib	WBRT	No difference in OS
Ma <i>et al.</i> , 2009	II	21	NA	WBRT + gefitinib	–	ORR 86%; median OS 13 months; no significant grade 3 toxicity
Pesce <i>et al.</i> , 2012	II	59	NA	WBRT + gefitinib vs. WBRT + TMZ	–	Median OS 6.3 months (gefitinib arm), 4.9 months (TMZ arm); no relevant toxicity
Zeng <i>et al.</i> , 2012	Retrospective	90	NA	WBRT + gefitinib	Gefitinib	Higher ORR and OS with WBRT + gefitinib
Luo <i>et al.</i> , 2015	Meta-analysis	980 (8 trials)	NA	Radiotherapy + TKI (TKI group)	Radiotherapy or radiotherapy + chemotherapy (non-TKI group)	Higher RR, CNS-TTP and OS in radiotherapy + TKI group; no difference in serious AEs
Jiang <i>et al.</i> , 2016	Meta-analysis	1,552 (15 trials)	Variable among 15 studies	Radiotherapy + TKI	Radiotherapy or radiotherapy + chemotherapy	Higher RR, DCR, CNS-TTP and OS in radiotherapy + TKI group; increased rate of any grade AEs

AEs, adverse events; CNS-TTP, time to central nervous system progression; DCR, disease control; EGFR, epidermal growth factor receptor; IDCR, intracranial disease control, NA, not available; ORR, overall response rate; OS, overall survival; RR, response rate; SRS, stereotactic radio surgery; TKI, tyrosine kinase inhibitor; TMZ, temozolomide; WBRT, whole brain radio therapy.

as part of multimodality treatment is not clarified yet. Therefore, clinical trials that include patients with BM are warranted to help clarify the optimal timing of TKIs and cranial radiotherapy in NSCLC, with the view to reserve neurocognitive function and improve clinical outcomes.

Acknowledgements

None.

Footnote

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

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Cite this article as: Economopoulou P, Mountzios G. Non-small cell lung cancer (NSCLC) and central nervous system (CNS) metastases: role of tyrosine kinase inhibitors (TKIs) and evidence in favor or against their use with concurrent cranial radiotherapy. *Transl Lung Cancer Res* 2016;5(6):588-598. doi: 10.21037/tlcr.2016.12.06

Management of non-small cell lung cancer with *EGFR* mutation: the role of radiotherapy in the era of tyrosine kinase inhibitor therapy—opportunities and challenges

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Contributions: (I) Conception and design: S Ma; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: In recent years, the treatment of advanced non-small cell lung cancer (NSCLC) was greatly promoted by the discovery of oncogenic drivers and the development of targeted therapies specific for these drivers. Somatic mutations in epidermal growth factor receptor (EGFR) are the most common type in patients with NSCLC. Small-molecule tyrosine kinase inhibitor (TKI) targeting EGFR produced relatively high response rate and long duration with acceptable toxicity profile. Also, the life expectancy in patients with active *EGFR* mutation has been significantly prolonged than the past. Additionally, evolution of advanced imaging and radiation techniques has expanded the indications for radiotherapy in complex clinical situation. All of those factors contributed to the widely use of radiotherapy for advanced NSCLC treated with TKI therapy. In this review, we will discuss how to integrate radiotherapy into the comprehensive treatment of patients with TKI therapy in order to maximize the therapeutics effect.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR); tyrosine kinase inhibitor (TKI); radiotherapy

Submitted Sep 01, 2017. Accepted for publication Sep 13, 2017.

doi: 10.21037/jtd.2017.09.67

View this article at: <http://dx.doi.org/10.21037/jtd.2017.09.67>

Background

Lung cancer is the leading cause of cancer-related deaths worldwide that constitute a significant global health burden. In 2017, it is estimated that there will be 222,500 new cases of lung and bronchus cancer and an estimate of 155,870 people will die of this disease in the United States (1). The situation is more serious in China because of the massive population and huge cigarette consumption; according to the cancer statistics released by the national central cancer registry of China in 2016, the estimated new cases and deaths of lung cancer per year were 733,300 and 610,200 in

the last decade (2). The overall prognosis of lung cancer is poor due to late-stage detection and ineffective therapies. Approximately 50–60% of the patients are with advanced stages that have no chance of receiving radical surgery or chemoradiotherapy. In addition, cytotoxic chemotherapy agents and combinations yielded low response rates, high toxicity rates, and limited improvements in survival although progress has been made over the past years at a modest pace. In this context, radiotherapy is generally used as a means of palliative care in this setting (3).

Recently, with new advances including the discovery of

oncogenic drivers and therapies specific for these drivers in non-small cell lung cancer (NSCLC), the application of oral small-molecule tyrosine kinase inhibitor (TKI) targeting these oncogenes was increased in clinic practice, which produced relatively high response rate and long duration with acceptable toxicity profile. Furthermore, the life expectancy in these patients has been significantly prolonged than those in the past with treatment of chemotherapy alone (4,5). In addition, evolution of advanced imaging and radiation techniques has also expanded the indications for radiotherapy in complex clinical situation (6). All of those factors contributed to the widely use of radiotherapy for advanced NSCLC treated with TKI therapy. In this review, we will discuss how to integrate radiotherapy into the comprehensive treatment of patients with TKI therapy in order to maximize the therapeutics effect.

Historical and current perspectives of epidermal growth factor receptor (EGFR) TKI therapy in NSCLC

In the last decade, management of advanced NSCLC has evolved toward stratification of patients based on oncogenic drivers, such as *EGFR* mutation, anaplastic lymphoma kinase (*ALK*), *ROS1* rearrangement etc. (7). Somatic mutations in *EGFR* are the most common type in patients with NSCLC. The overall prevalence for *EGFR* mutations was about 30%, ranging from 38.4% in China to 14.1% in Europe. Besides ethnicity (Western/Asian), other factors, included smoking status (yes/no), sex (male/female) and histology (adenocarcinoma/squamous cell carcinoma), also affected the incidence rates of *EGFR* mutations (8).

The first-generation (gefitinib, erlotinib and icotinib) and second-generation (afatinib) *EGFR* TKIs are now standard as the first-line treatment for patients with advanced *EGFR*-mutated NSCLC. For patients with active *EGFR* mutations, TKIs produced high response rates up to 75% and improved progression-free survival (PFS) to 9–13 months as compared with chemotherapy in randomized trials (4,9–11). However, majority of the patients developed acquired drug resistance after initial response to TKI, and the median overall survival in those patients was estimated to 30 months. Studies of tumors biopsied at the time of disease progression have elucidated mechanisms of acquired resistance, in which the development of T790M mutation is the most common resistance mechanism (approximately 50–60%) (12,13). That discovery has led to the development of

third-generation TKI, osimertinib, which has shown to be superior to standard platinum/pemetrexed chemotherapy in patients whose tumors have developed T790M mutations. Among patients receiving osimertinib, the response rate and median PFS were about 71% and 10.1 months in phase 3 trial (AURA3) (14). Although the overall survival was not available because of immature data, it can be expected that survival will be further extended in this population.

In the past, the life expectancy of most patients with metastatic NSCLC is measured in months; radiotherapy is frequently used to palliate symptoms with a low total dose and is often administrated relatively late. With the prolonged survival duration of those patients receiving TKI therapy, the timing and dose of radiotherapy need to be redefined in order to optimize the delivery of radiotherapy.

Palliative radiotherapy in advanced NSCLC treated with EGFR TKI

As for the patients with advanced stage NSCLC, various disease related symptoms often developed at diagnosis due to diverse causes such as superior vena cava obstruction, airway obstruction, bone destruction and brain metastasis. Generally, palliative radiotherapy is administrated immediately in this setting in order to quickly relieve symptoms and improve quality of life (QOL), and symptoms improvement rates of 50–80% were reported in literatures (15,16). Of note, systemic treatment is often delayed until the end of radiotherapy, with the concerns of the increased toxicities of combined modalities. In patients with active *EGFR* mutation, TKI therapy produces a high response rate up to 75%, which is comparable to the efficacy of palliative radiotherapy. In addition, the shorter time of response to TKI therapy may be useful for early symptom improvement for these patients. Imai *et al.* compared the efficacies of radiotherapy and TKI in NSCLC patient harbored sensitive *EGFR* mutation, based on the RECIST criteria (17). In this study, 17 patients were administrated with radiotherapy and 32 patients received TKI therapy. As to their report, the response rates were 64.7% and 81.3% and the time-to-partial response were 40 and 20 days respectively, with evaluation limited to patients with a response. Other studies have also reported that the median time to symptomatic relief was observed within 2–3 weeks for patients treated with *EGFR* TKIs (18,19). These results suggest that TKI can be considered as the first choice if the primary goal was to achieve prompt symptomatic relief. It is unclear whether

delivery of concomitant radiotherapy can be resulted in better outcomes, but such an approach of combined treatment deserved additional studies to explore, considered of the favorable toxicity profile when radiotherapy combined with TKI therapy reported in literatures (20,21).

With regard to the radiation prescription, a low dose and shorter overall treatment time are preferred in recent clinical guidelines of American Society for Radiation Oncology (ASTRO) and National Comprehensive Cancer Network (NCCN), due to lower costs and greater convenience in the face of short life expectancy. However, in a recent study based on a national population cohort of metastatic NSCLC administrated with palliative radiotherapy, investigators found that a substantial proportion of patients received a greater number of treatments and higher doses than supported by current evidence (22). This observation reflected that providers may believe that intensive treatment can be delivered with minimal toxicity and will bring additional benefit from even higher doses, although such willingness is not supported by available data. Because of good response to TKI therapy, patients with active *EGFR* mutation can be considered as the candidate to test such tentative idea. In addition, the disease status of some patients became limited after TKI therapy, defined as induced oligo-metastases. Possibly, those patients have the chance to receive curative therapies such as surgery, ablation, or stereotactic body radiation therapy (SBRT). In a recent study aimed to evaluate the pattern of failure in patients receiving TKI therapy, about 20% of the patients were judged feasible for consolidation SBRT (23).

Radiotherapy at the time of disease progression after TKI therapy

In patients received first-line TKI therapy, acquired drug resistance was developed inevitably despite dramatically response initially. In clinical practice, several failure modes were conceived in order to favor strategies for subsequent management. In Yang's study, three modes of dramatic, gradual and local progression were proposed according to specific criteria derived from clinical factors, and continuation of TKI plus local intervention was recommended for the last situation (24). Weickhardt *et al.* investigated the benefits of local ablative therapy to limited systemic disease progression in patients who received TKI therapy and a second PFS of 6 months was observed (25). In another study considering the role of local therapy

in patients with acquired resistance, Yu *et al.* reported that the time to progression after local therapy was 10 months and the median time from local therapy until a change in systemic therapy was 22 months (26). Although encouraging results were reported in these studies, it should be noted that the patients enrolled in the studies were strictly selected, and the proportion of such patients was not high accounting for the whole population treated with *EGFR* TKIs. Also, because of the inherent limitations in retrospective studies, the true benefit of local radiotherapy combined with continuation of TKI therapy argue for additional studies with standardized enrollment and research process in a prospective fragment.

Early intervention of radiotherapy in TKI therapy

Accumulating data revealed how tumors become resistant to *EGFR* TKI. The most common known mechanism is the acquisition of T790M that renders the kinase resistant to the first-line TKI (27,28). Studies showed that T790M existed at a low frequency within the tumor cells pretreatment and became the dominant clone after selection pressure of *EGFR*-TKI therapy (29). In addition, preclinical studies also demonstrated that a second mutation of T790M could be successfully induced in PC-9 lung cancer cells after about 120 days culture with TKI (30). These results indicated that both mechanisms of *de novo* and induced T790M could be present in the course of TKI treatment. In fact, cancer cells harbored T790M exhibited enhanced sensitivity to radiation (31), suggesting the potential role of radiotherapy in the management of *EGFR*-TKI related resistance. If intervention of radiation was administrated at the time of best response of TKI therapy, instead of disease progression, it may benefit patients by reducing the chance or delay the time of T790M-mediated *EGFR* TKI resistance. Meanwhile, radiotherapy provides opportunities of reducing systemic reseeding from the growth of resistant clones harbored T790M in the original sites. Actually, there were several clinical reports that supported such deduction. In a study of 25 patients with IIIb/IV NSCLC who responded to upfront TKI treatment, concomitant radiotherapy of 40–50 Gy in 16–20 fractions were delivered with tomotherapy for individual metastatic lesions (32). The overall response rate was 84.0% and the median PFS was 16 months. The 3-year overall survival rate was 62.5% and toxicities were generally tolerated. These encouraging results indicated that radiotherapy might aid

expansion the effectiveness of TKI therapy in those patients who are responding to TKI treatment. In another two studies using TKI combined with radiotherapy in stage III/IV NSCLC, although enrolled patients was not selected based on the *EGFR* mutation status, the median PFS of 10–14 months and survival time of 20–22 months were observed with acceptable toxicities, indicated the feasibility of targeted therapy combined with advanced radiotherapy in clinical practice (33,34). Recently, we launched a phase II trial of hypofractionated radiotherapy for limited metastatic NSCLC harboring sensitizing *EGFR* mutations, the inclusion patients are required to be oligometastatic disease (≤ 5 discrete lesions of disease, exclusive of the brain metastases) after 3 months of TKI therapy, evaluated by PET/CT scan. The scheduled time of radiotherapy is 3 months after TKI therapy in patients responded to TKI, and the primary objective is to extent PFS to 16 months.

Now, for patients with active *EGFR* mutations who progress during or after first-line targeted therapy, subsequent therapy depends on the specific genetic alteration, the histologic subtype, and whether the patients have symptoms. Osimertinib is recommended for patients with T790M positive. Of interest, we recently revealed the correlations of the disease failure sites with the frequency and abundance of T790M mutations in 314 patients who progressed during TKI treatment. In these patients, plasma T790M mutations were detected in 46.8% of the populations by droplet digital PCR, and T790M mutation was associated with extensive progression of the tumor, suggesting that NSCLC tumor cells with acquired T790M mutation may indicate distinct natural history and are with capability of cancer cell invasion and migration. Other studies reported that plasma T790M mutation could be detected approximately at 2.2 months prior to clinical progression, indicating that the spread of tumor cell with T790M mutation in circulation might be an early event in the course of disease metastasis (35,36). Upon the sustaining TKI exposure, T790M mutation is more likely to develop and gain the upper hand in the original disease sites, and then the growth of resistant T790M cancer cell clones can systemically reseed and finally lead to distant failures in new sites of disease. Therefore, early intervention to eradicate residual disease after TKI therapy, which may contain low abundance of *de novo* or acquired T790M mutation, can provide an opportunity to reduce the risk of subsequent extensive progression. Taking together, the value of early intervention in patients treated with TKI therapy is worth to be further investigated.

Management of brain metastasis in patients with *EGFR* mutation

Brain metastasis and EGFR mutation

Many patients with NSCLC have brain metastases (30–50%), which is one of the most devastating complications threatening to life (37,38). Of note, the risk of brain metastases is relatively high in patients with *EGFR* mutation at the time of diagnosis, as well as during the course of follow up in those who administrated with surgery. Shin *et al.* reported a dramatic correlation of *EGFR* mutation status and brain metastasis (adjusted odds ratio =3.83, $P=0.001$) in 314 patients with testing of *EGFR* mutation and brain magnetic resonance imaging at diagnosis (39). In this study, they also found that, in a subgroup analysis of 133 patients treated with surgical resection, *EGFR* mutation status was a poor prognostic factor for the risk of brain metastasis [hazard ratio (HR) =4.49, $P=0.026$] after adjustment for pathologic N stage. In addition, during the course of TKI therapy in advanced NSCLC, about 30% of the treatment failure was the present with new lesions or progression of original sites intracranial, which may be related to the low drug concentration of first-line TKIs in the cerebrospinal fluid and the prolonged survival in those patients. Because of the high percentage and the devastating outcomes of brain metastases, how to optimize the management of brain metastasis has become a clinical challenge of the comprehensive treatment for patients with *EGFR* mutation.

Whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS)

For patients with brain metastases, both WBRT and SRS can be considered, mainly depend on the number/volume of brain metastases and the performance status of the patient. Generally, WBRT is recommended for multiple metastases (e.g., >3) and SRS is preferred for limited brain metastases. Accumulating evidences have indicated that TKI is also efficient for brain metastases in patients with *EGFR* mutation. Chinese Thoracic Oncology Group (CTONG) 0803 showed that single-agent erlotinib was active and well tolerated in patients with asymptomatic brain metastases, the median PFS and overall survival were 15.2 and 18.9 months for patients with activating *EGFR* mutation (40). Encouraged by these findings, and the concern of the potential neurocognitive function in the use of WBRT, CTONG 1201 was initiated to compare the efficacy of TKI

(icotinib) versus WBRT with or without chemotherapy in NSCLC patients with *EGFR* mutation, who were naive to treatment with EGFR-TKIs or radiotherapy, and had at least three metastatic brain lesions. In this phase III prospective study, 176 patients were recruited and 158 cases were used for the final analysis. The results showed intracranial disease control rates of 85% and 67%, and median intracranial PFS of 10.0 and 4.8 months in the icotinib and WBRT groups, respectively. In addition, the evaluation of cognitive ability was available in 59 patients based on mini-mental state examination (MMSE) questionnaires, and no difference was found in these two groups. Also, there were no significant differences between groups for overall survival or time to increased brain metastases symptoms (41). Although the primary endpoint, intracranial PFS, was met in this study, there were some deficiencies in the design of the trial, for example, a combination therapy group was lacking.

It is well known that symptom control and QOL are the primary goal in the management of advanced NSCLC. Therefore, the phase III trial only provided evidences that first-line TKI might be considered as a therapeutic option in the treatment of EGFR-mutant NSCLC with brain metastases, and WBRT is still the standard of care in this setting. Actually, EGFR TKI and WBRT should be complementary rather than competitive, how to combination of both to make the patient live better is the most of important. Very recently, Magnuson *et al.* reported a multi-institutional retrospective analysis aiming to determine the optimal management of patients with EGFR-mutant NSCLC who develop brain metastases, and three modes of combination of TKI and radiotherapy was investigated (42). Their results showed that the median overall survival in patients received SRS followed by TKI, WBRT followed by TKI, and TKI followed by SRS/WBRT were 46, 30, and 25 months, respectively, indicating that the use of upfront EGFR-TKI and deferral of radiotherapy were associated with inferior survival in this setting. Besides the longest overall survival, SRS followed by TKI provided the opportunity for patients to avoid the potential neurocognitive sequelae of WBRT. Concomitant use of TKI may have the advantage of a synergistic effect on the brain metastases, but at the price of possibly increased risk of neurotoxicity. Such attempt had been reported in a lot of retrospective and prospective studies, but often with small sample size (20). Primary outcomes in these studies varied and the data were measured and reported in a non-uniform way. So, it is still difficult to draw any conclusion

about the efficacy and safety based on current data, although some reports showed that WBRT concurrent with TKI does not seem to increase neurotoxicity. Taking together, appropriate timing of radiotherapy is critical in the management of EGFR mutant NSCLC, investigation of the use of TKI in combination with radiotherapy (WBRT/SRS) and optimal sequences between TKI and radiotherapy are warranted in future studies.

Prophylactic cranial irradiation (PCI)

PCI has been successfully used in patients with small-cell lung cancer in limited and extensive stage, which significantly reduced intracranial progression and prolonged over survival (43). However, the value of PCI in NSCLC remains controversial (44). No survival benefit and only decrease and/or delay of brain metastases were observed in many phase-III trials. The lack of survival benefit may be partially attributed to unintentionally selected patients with a high risk of brain metastasis. In addition, decline in tested and self-reported cognitive functioning after PCI in lung cancer were reported in a pooled secondary analysis of Radiation Therapy Oncology Group (RTOG) randomized trials 0212 and 0214 (45). To prevent these adverse early cognitive effects of cranial radiation, modern radiotherapy techniques [intensity-modulated radiation therapy (IMRT)] have been used for avoiding the hippocampal neural stem-cell niche during WBRT. RTOG 0933 was a single-arm phase II study of radiotherapy for brain metastasis, and the results from this study showed that hippocampal-avoidance WBRT was associated with preservation of memory and QOL as compared with historical series (46). Notable, patient with *EGFR* mutation has the relatively high risk of developing brain metastases, and the reported intracranial progression during the course of TKI therapy is approximately 30% (39). Therefore, it is interesting to explore the role of PCI in the patients treated with TKIs, provided that preservation of memory and QOL can be ensured with modern radiotherapy techniques.

Management of local advanced NSCLC with TKI and radiotherapy

The combination of chemotherapy and radiotherapy is the standard of care in the management of locally advanced NSCLC. Concurrent chemoradiotherapy is the preferred approach for patients with good performance status; but

the improved therapeutic effect may be at the cost with increased toxicities. Currently, the clinical outcomes are still unsatisfactory, and the 5-year survival rate of is approximately 20%. In recent published studies, attempts to improvement of the radiation dose (RTOG 0617) and use of a new generation of chemotherapy regimen (PROCLAIM) failed to demonstrate survival benefits compared with concurrent platinum-based doublet chemoradiotherapy conventionally used in clinical practice (47,48). Uncertainties resulted from high treatment-related toxicities and poor completion rates of chemoradiotherapy in these trials should be rethink profoundly in future studies, and further improvement in locally advanced NSCLC will require the development of more effective combined modality therapies with low toxicities.

The rational for integration of EGFR TKI in the comprehensive treatment of locally advanced NSCLC includes high expression of EGFR in 40–80% NSCLC and autophosphorylation of the EGFR induced by irradiation (49). Preclinical studies showed that EGFR TKI, such as gefitinib and erlotinib, have radiosensitizing effects at multiple levels including cell cycle arrest, apoptosis, accelerated repopulation and DNA damage repair (50). However, in previous clinical studies, incorporation of TKI in the combined chemoradiotherapy for locally advanced NSCLC was not associated with improved treatment outcomes (51); possible explanations include the cell cycle specific antagonism when combined with concurrent chemotherapy and the unselected patients in these trials. Recently, RECEL trial reported the preliminary results in 2017 American Society of Clinical Oncology (ASCO) annual meeting. This was a multicenter, randomized, open-label, phase II trial of erlotinib versus etoposide plus cisplatin with concurrent radiotherapy in unresectable stage III NSCLC with *EGFR* activating mutation. The median PFS in this trial was significantly improved in the erlotinib group (n=20) compared with the control group (n=21) (27.9 vs. 6.4 months, HR 0.053, P<0.001). Both arms had same incidence of adverse effects (CTCAE grade >1), and most common sAE (grade >3) was rash (20%, 3/15) and hematological toxicity (26.7%, 4/15), respectively. Given the excellent outcomes in advanced NSCLC treated with EGFR TKIs, it is not surprising to have obtained such results in this trial. The questions need to be answered in future studies include the best duration of TKI therapy, the optimal combination algorithms of radiotherapy and TKI, and the potential beneficial population based on molecular characterization.

Conclusions

In NSCLC, patients with active *EGFR* mutation belong to a special group who has particular biological behavior and clinical management algorithms. Although wonderful outcomes of immediate responded to targeted therapies, and new generations of targeted drugs continued to be developed, all of these drugs are inevitably faced with the problem of resistance because of the tumor heterogeneity and evolutionary characteristics, and the inherent limitations of targeted treatment strategy. Advances in functional imaging and cutting-edge radiation techniques greatly expand the application field of radiotherapy in advanced NSCLC. Increasing evidences have been showed that integration of modern radiotherapy in the management of patients treated with EGFR TKI will be contributed to the improvement of treatment outcomes, early intervention of radiotherapy for limited disease, optimization the sequence of TKI and cranial radiotherapy, PCI and combination of TKI and thoracic radiotherapy in locally advanced NSCLC deserve further research in future studies.

Acknowledgements

Funding: This paper was supported by grants from the National Nature Science Foundation of China (grant no. 81301927), Zhejiang Provincial Nature Science Foundation (grant no. LY13H160023) and Hangzhou Medical Major Disease Project (grant no. 20130733Q03).

Footnote

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

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Cite this article as: Xia B, Zhang S, Ma S. Management of non-small cell lung cancer with *EGFR* mutation: the role of radiotherapy in the era of tyrosine kinase inhibitor therapy—opportunities and challenges. *J Thorac Dis* 2017;9(9):3385-3393. doi: 10.21037/jtd.2017.09.67

Is post-operative radiotherapy of any benefit after R0 resection for N2 disease?

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Submitted Jun 29, 2014. Accepted for publication Jul 04, 2015.

doi: 10.3978/j.issn.2218-6751.2015.07.01

View this article at: <http://dx.doi.org/10.3978/j.issn.2218-6751.2015.07.01>

This is another paper in a recent and growing trend of papers that takes a very large database and by the sheer basis of numbers tries to answer what is a very common posed question (1). Importantly, this particular question may not be answerable using a smaller more granular or detailed database.

Perhaps the three most important questions that are asked in tumor conference when a patient is to be considered for adjuvant radiotherapy after undergoing a completed-resected pathologically N2 non-small cell lung cancer is: (I) how many N2 stations were involved? (II) Is the cell type adenocarcinoma or squamous cell carcinoma? And (III) were the lymph nodes completely removed or only biopsied (sampled)?

Unfortunately, none of these particular data points are contained in the National Cancer Data Base. However, I do not think this fact detracts from the study for several reasons. First, the number of N2 and/or N1 stations is often biased by the surgeon or by his operative technique. Even the accuracy of lymph node count is dubious. Second, the definition of “complete thoracic lymphadenectomy” compared to “sampling” are mains unclear despite the fact that I argue adamantly for the former every day.

Given these caveats then a more detailed database may not shed any more light on the answer to this question. The sheer number of patients in the study may allow for the conclusions to remain valid. And, if so, then it is of significant clinical importance since it is a commonly posed question for patients. This study has a chance to have significant impact and be commonly cited.

Finally, the authors are from a group that is well-known for delivering both high quality surgery and complicated statistical analyses of surgical data. This provides even more credence for the paper’s conclusions. It is refreshing to have some science and data provided to a common question that is too often answered with opinions and dogma that we often hear at our tumor boards, i.e., “more than one N2 stations we radiate, if there is only one N2 station positive for cancer then we do not—and we radiate only those with squamous cell cancer.”

Furthermore, these conclusions make sense since another large study using the SEER database (2) have shown a benefit of PORT for those with III A (N2) disease as opposed to harm with PORT for those with N1. Since the LUNGART study is several years away from completion, this study is our best data and for now may persuade many of us to recommend PORT for those with completely resected N2.

Acknowledgements

Dr. Robinson and colleagues are to be congratulated for presenting an interesting paper.

Footnote

Conflicts of Interest: The authors disclose the following relationships: Intuitive Surgical—teacher, Ethicon—teacher, Covidien—teacher and Community Health Systems—consultant, KCI— teacher.

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Cite this article as: Cerfolio RJ, Estes JH. Is post-operative radiotherapy of any benefit after R0 resection for N2 disease? *Transl Lung Cancer Res* 2015;4(5):665-666. doi: 10.3978/j.issn.2218-6751.2015.07.01

Response to “Is post-operative radiotherapy of any benefit after R0 resection for N2 disease?”

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Submitted Aug 24, 2015. Accepted for publication Aug 25, 2015.

doi: 10.3978/j.issn.2218-6751.2015.08.12

View this article at: <http://dx.doi.org/10.3978/j.issn.2218-6751.2015.08.12>

We thank Drs Cerfolio and Estes (1) for their comments in regard to our recently published analysis from the National Cancer Data Base (NCDB) exploring the utility of post-operative radiotherapy (PORT) in completely resected N2 non-small cell lung cancer (NSCLC) treated with adjuvant chemotherapy (2). As they note, while the strength of such a multi-institutional database lies in its numbers (in this case, more than 4,000 patients), there is an expected loss of data fidelity and granularity. For example, in our analysis we had a limited ability to explore questions of lymph node station involvement, number of nodes, or completeness of lymph node sampling due to incomplete or completely missing data. As such, we could not control for these variables in our multivariate modeling. However, with respect to questions of lymph node involvement or sampling, it would be expected that those patients with less favorable features (incomplete dissection, more lymph node involvement, etc.) would be more likely to receive PORT. If it were possible to account for this likely stacking of less favorable patients in the PORT group, it seems possible that we may have seen an even larger benefit to PORT. Nonetheless, such an imbalance could not reverse the survival curves, and therefore we believe our overall conclusions remain

sound. Additionally, we appreciate Dr. Cerfolio and Estes' kind comments regarding the importance of our analysis in the absence of randomized data, and echo our support for randomized trials such as Lung ART.

Acknowledgements

None.

Footnote

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

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Cite this article as: Robinson CG, Patel AP, DeWees T, Morgensztern D, Bradley JD, Puri V. Response to “Is post-operative radiotherapy of any benefit after R0 resection for N2 disease?” *Transl Lung Cancer Res* 2015;4(5):667. doi: 10.3978/j.issn.2218-6751.2015.08.12

Salvage surgery after high-dose radiotherapy

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Abstract: Salvage surgery is a relatively new entity in thoracic surgery and oncology. Salvage resection after radiotherapy refers to surgery as only remaining therapeutic option in patients who were treated with high-dose stereotactic radiotherapy (SRT) for early-stage lung cancer or full-dose chemoradiation for locally advanced lung cancer. Indications include locally progressive tumors, recurrent local or locoregional disease, or specific complications after radiotherapy such as lung abscesses or infected, necrotic cavities. Small, retrospective series demonstrate that salvage surgery after high-dose radiotherapy is feasible and may yield good long-term results. A clear distinction should be made between salvage surgery after SRT for early-stage lung cancer and salvage procedures after full-dose chemoradiation for lung cancers with locoregional extension into the mediastinum. Salvage surgery after SRT may be rather straightforward and in specific cases even feasible by a minimally invasive approach. In contrast, surgery after a full dose of chemoradiation delivered several months or years earlier, can be quite challenging and the dissection of the pulmonary artery and mediastinal lymph nodes technically demanding. Due to the more central irradiation an intrapericardial dissection is often required. To prevent a bronchopleural fistula protection of the bronchial stump with well-vascularized flaps is recommended. Each individual patient in whom salvage surgery is considered, should be discussed thoroughly within a multidisciplinary board, detailed cardiopulmonary functional evaluation is required, and the operation should be performed by an experienced team including a thoracic surgeon, anaesthesiologist and intensive care physician. At the present time only retrospective series are available. Carefully designed prospective studies are necessary to more precisely define indications and results of salvage surgery not only after SRT for peripherally localized lesions but also following full-dose chemoradiation for locoregionally advanced disease.

Keywords: Non-small cell lung cancer (NSCLC); stereotactic radiotherapy (SRT); salvage surgery; early-stage lung cancer; locally advanced lung cancer

Submitted Jan 17, 2017. Accepted for publication Feb 09, 2017.

doi: 10.21037/jtd.2017.03.88

View this article at: <http://dx.doi.org/10.21037/jtd.2017.03.88>

Introduction

In 1895, X-rays were discovered by a German physicist, Wilhelm Conrad Rontgen. Soon thereafter their diagnostic but also their therapeutic potential was discovered. Ever since that time, they have been indispensable in the diagnosis and treatment of cancer. At the present time, surgery and radiotherapy are the most important local

treatment modalities for lung cancer (1). Specific radiation delivery is an ever changing domain in the therapeutic armamentarium for lung cancer and recently, specific techniques have been developed allowing high-dose delivery to tumor cells with sparing of critical organs in close contact to the primary tumor (1).

At the present day, some subgroups of early-stage non-small cell lung cancer (NSCLC), especially those with a

compromised cardiopulmonary function, may be treated by stereotactic radiotherapy (SRT), also called stereotactic body radiation therapy (SBRT), stereotactic ablative radiotherapy (SABR), or stereotactic radiosurgery (SRS). The latter term is confusing and should be avoided as surgical treatment is not a part of this specific therapy. For the sake of simplicity in this manuscript we prefer to use the term SRT which is currently considered to be an alternative to surgical treatment.

Treatment of locally advanced NSCLC remains highly controversial, mainly due to the fact that this represents a very heterogeneous population ranging from unexpected nodal involvement to bulky mediastinal lymph node metastases which do not qualify for surgical resection (2). The main treatment options comprise definitive concurrent chemoradiation which has become the standard treatment, sequential chemoradiation, induction chemotherapy followed by surgery or radiotherapy, and induction concurrent chemoradiation followed by surgery.

For those patients having persistent or recurrent disease after high-dose SRT or after full chemoradiation, salvage surgery has emerged as a possible treatment option (3). Salvage surgery is defined as surgical resection of persistent or recurrent primary lung cancer after previous local treatment without surgery, in case of urgency such as hemoptysis, bronchial stenosis, abscess cavity or empyema, or as therapy for chronic bronchopleural or bronchopulmonary fistulas (*Table 1*). It is considered to be technically more difficult due to post-radiation inflammation and fibrosis.

Every patient qualifying for salvage surgery should undergo a thorough cardiopulmonary evaluation and be discussed within a dedicated multidisciplinary tumor board, especially when a pneumonectomy or intrapericardial dissection is anticipated. Up till now, only limited data have been published. A best evidence topic on salvage surgical interventions after high-dose radiotherapy was published by Schreiner and colleagues in 2015 (4). In total, 4 out of 9 reports provided the best available evidence but all of them were retrospective. In 47 patients, 48 salvage resections were performed after high-dose radiotherapy, SRT or chemoradiation. There were 4 sublobar resections, 32 (bi) lobectomies (1 sleeve resection), and 12 pneumonectomies. Mean postoperative complication rate extracted from 4 studies was 42.5%. Median survival time ranged from 9 till 30 months. The authors concluded that salvage surgery may be considered a worthwhile treatment option with low mortality, acceptable morbidity and relatively good

survival.

In the present review, salvage surgery after high-dose radiotherapy is discussed, making a clear distinction between surgical resection after SRT for early-stage lung cancer, and surgery after combined modality therapy for locoregionally advanced disease.

Salvage surgery in early-stage lung cancer

Approximately 20% of patients diagnosed with NSCLC have early-stage lung cancer. In the recently introduced 8th TNM edition further subdivisions are made in the T (tumor) descriptor with increments of 1 cm for T1 and T2 lung cancer, as prognosis is best for the smallest lung cancers (5). According to the guidelines of the European Society of Medical Oncology (ESMO) lobectomy is still considered the standard surgical treatment for early-stage lung cancer (6). In patients who are unable to undergo a lobectomy, but fit for surgery, sublobar resections represent an alternative option and are preferred over radiotherapy (7,8). In total, 10% to 15% of the patients, diagnosed with early-stage NSCLC are medically unfit for surgery or decline surgery and these patients are usually treated with SRT (9). An ultra-high dose is administered consisting of ablative fractions of radiation to a target, which allows for maximizing cell-killing effect on the primary tumor (1). In contrast to conventional irradiation, which is delivered daily for six to eight weeks, SRT is typically administered in one to ten fractions in doses of 6–34 Gy per fraction (10). Good results have been reported with SRT in medically inoperable patients with a local control rate of 80–100% and 3-year survival of 40–80% (10,11). However, it should be noted that a histological diagnosis is not obtained in every case, lymph node evaluation and clinical staging are less rigorous, and no universally accepted criteria are available for response evaluation (12). In this way, local control is often defined as “absence of progressive disease” in contrast to a complete surgical resection which implies that there is no remaining disease (13–15).

The promising results of SRT in medically unfit patients stimulated further research of SRT in patients with a good cardiopulmonary function as alternative treatment to surgical resection. Onishi *et al.* investigated SRT in stage I and II patients who were medically fit but refused surgery (16). SRT (45–72.5 Gy in 3–10 fractions) was associated with a 5-year cumulative local control rate of 92% for T1 tumors and 73% for T2 tumors. Five-year overall survival (OS) rates were 72% for stage IA and 62%

Table 1 Indications for salvage surgery

Early-stage NSCLC after SRT
Persisting local disease
Local recurrence
Progressive disease
Complications: lung abscess, pulmonary fistula
Locoregionally advanced NSCLC after full-dose chemoradiation
Persisting locoregional disease
Locoregional recurrence
Complications: hemoptysis, lung abscess, empyema, bronchopleural fistula

NSCLC, non-small cell lung cancer; SRT, stereotactic radiotherapy.



Figure 1 Chest computed tomographic scan demonstrating a right upper lobe cancer, clinical stage IA, in an 81-year-old patient treated with stereotactic radiotherapy. This patient was initially considered functionally inoperable.

for stage IB, respectively, similar to outcomes reported in surgical series (16). The U.S. STARS (NCT 00840749) and Dutch ROSEL (NCT00687986) trials were randomized controlled trials comparing surgical resection to SRT but closed early due to poor accrual. Data were pooled in a subsequent analysis by Chang *et al.* showing a significant 3-year OS advantage in favor of SRT (95% *vs.* 79%; $P=0.037$) in the 58 included patients (17). Disease-free survival was not different between both groups. The authors state that these data suggest at least clinical equipoise between the two treatment modalities. Several Letters to the Editor pointed out that results cannot be generalized as mortality in the surgical arm was unacceptably high, detailed histology was not obtained in every case and a valid

comparison of locoregional control between surgery and SRT is not possible (14,18-23). Further randomised studies are currently ongoing mainly recruiting patients at higher risk for surgical resection (24).

A recent question that emerged and which is currently discussed at major lung cancer conferences is how to treat locoregional recurrences after SRT and whether surgery may play a role as subsequent treatment. As mentioned before, specific diagnosis of persisting or recurrent tumor growth after SRT is challenging as an inflammatory reaction is induced by SRT giving rise to pneumonitis and fibrosis at the level of the primary tumor site. The appearance of a zone of consolidation on chest computed tomography (CT) could be radiation pneumonitis, radiation fibrosis, persisting tumor growth or local recurrence (25). Tumor serum markers as carcinoembryonic antigen (CEA) and fluorodeoxyglucose positron-emission tomographic (FDG-PET) images may be helpful in the differential diagnosis although increased FDG-uptake may persist up to 2 years after SRT without evidence of recurrence (26,27).

Reported local recurrence rate after SRT for early-stage NSCLC mounts to 20% after 3 years (10). A larger tumor size and a lower retention index on FDG-PET scanning are risk factors for recurrence (28,29). Time between SRT and local recurrence is highly variable, ranging from 9 to 89 months (30). Therefore, close follow-up after SRT is indispensable.

Treatment options for local recurrence after SRT include salvage surgery, systemic chemotherapy, targeted agents, chemoradiation, repeat high-dose radiotherapy or best supportive therapy in patients with poor performance status (30-32). Indications for salvage surgery are listed in *Table 1* (*Figures 1,2*). Reassessment of cardiopulmonary functional operability at the time of local recurrence is very important. Rather surprisingly, patients undergoing salvage surgery may have been considered inoperable at the time of SRT as was the case in the patient described in *Figures 1,2*, and in 3 out of 12 patients in the series reported by Hamaji and colleagues (30). On the other hand, operable patients may become functionally inoperable over time giving rise to a high operative risk, and in these cases alternative options have to be considered (32).

Regarding literature data only retrospective series are available. Hamaji *et al.* reported a series of 49 patients with isolated local recurrence after SRT (30). Best supportive care was administered in 29 patients, chemoradiation in 8, and 12 patients underwent salvage surgery. For the latter subgroup 5-year OS was 79.5% calculated from local

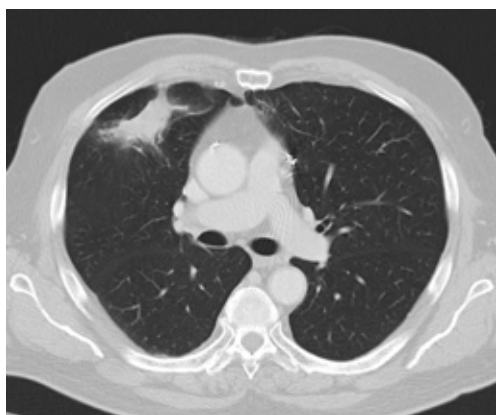


Figure 2 Chest computed tomographic scan of the same patient showing progressive disease 18 months later. Salvage bilobectomy was necessary to obtain a complete resection. There were no postoperative complications.

recurrence on.

Sugimoto *et al.* reported a right upper lobectomy by video-assisted thoracic surgery (VATS) for a peripheral stage I NSCLC after radiotherapy (33). Adhesions were limited and easily divided. Central structures were intact, probably because of peripheral and not central irradiation. Neri and colleagues reported 7 patients who underwent salvage surgery after SRT for primary NSCLC or lung metastases (26). Median time period between SRT and salvage surgery was 10 months. There were 6 lobectomies and 1 segmentectomy; 2 patients had incomplete resections. The distance from the pleura to the tumor ranged from 5 to 30 mm. There were no technical difficulties and complications consisted of 1 pulmonary fistula and 4 cases of post-radiotherapy pneumonitis. Allibhai *et al.* reported a small but interesting series as detailed pathological examination was available (34). Out of a prospective series of 209 patients who underwent SRT for early-stage NSCLC 4 had salvage surgery consisting of lobectomy and nodal sampling. In one patient a partial chest wall resection was necessary. Pleural adhesions were encountered in every case but there were no significant technical complications. No viable tumor was found in one patient but the others had 5–65% viable cancer cells. After a median follow-up of 30 months there was no evidence of disease. Although in the cases of Hamaji, Sugimoto and Neri, only limited pleural adhesions were present after SRT, more extensive adhesions were encountered by Allibhai and also in 2 out of 9 patients published by Versteegen, which led to conversion in one case (34,35). This may be due to a different location

of the primary lesion and therefore a low radiation dose to the ipsilateral bronchial tree (33,35).

In a cumulative review presented at the 2016 Annual Meeting of the American Association for Thoracic Surgery (AATS) in Baltimore, 37 patients from 4 institutions underwent salvage surgery for pulmonary lesions previously treated with SRT (36). Twenty-six patients had NSCLC and 11 lung metastases with a median disease-free survival of 19.2 months. Of interest, 8 patients (21.6%) were initially considered medically inoperable. Median time interval between SRT and surgery was 16.1 months (range, 6.4–104.0 months). Median survival time following surgery was 46.9 months and 3-year OS 70.1% (36).

In selected cases of oligometastatic disease salvage surgery may also be considered after discussion within a dedicated multidisciplinary team (37). Recently, we reported a case of salvage lung surgery in a patient with oligometastatic disease who initially presented with a femoral bone metastasis from NSCLC treated by osteosynthesis and local radiotherapy (38). Chemoradiation was administered to the primary lung cancer located in the right upper lobe. Because of isolated local recurrence in the upper lobe, salvage lobectomy was performed 18 months later. After present follow-up of 8 years there are no signs of recurrent disease. This case indicates that salvage surgery may even be indicated in exceptional and complex cases on the condition that a complete resection is obtained.

Salvage surgery in locoregionally advanced lung cancer

At the time of lung cancer diagnosis 30% of the patients present with locoregionally advanced disease comprising stages IIIA and IIIB which include quite heterogeneous patient populations (2,39). For this reason treatment of stage IIIA and IIIB NSCLC remains controversial and should be tailored to the individual patient after discussion within a multidisciplinary tumor board. As many patients have extensive mediastinal invasion, concurrent chemoradiation with a high radiotherapy dose (>59 Gy) has become standard treatment in this patient population (1). For potentially operable patients with N2 involvement or T3–4 superior sulcus tumors, induction chemoradiation consists of a locally applied dose of 30–50 Gy in combination with systemic cisplatin-based chemotherapy followed by surgery 4 to 8 weeks later when there is no progressive disease.

Isolated local relapse occurs in 24–35% of patients after definitive chemoradiation for locally advanced NSCLC (40).



Figure 3 Large abscess cavity colonized by bacteria and fungi in a 39-year-old patient who underwent full-dose chemoradiation 6 months earlier for a right upper lobe adenocarcinoma with mediastinal involvement. A right intrapericardial pneumonectomy became necessary.



Figure 4 Postoperative chest X-ray of the same patient demonstrating irrigation system after right intrapericardial pneumonectomy. There is one inflow drain at the top and 2 basal outflow drains.

There is no consensus on the most effective therapy of those recurrences and treatment options include repeat irradiation, systemic chemotherapy, chemoradiation, cryotherapy, radiofrequency ablation, watchful waiting and salvage surgery (41-43). In selected patients salvage surgery may improve survival if a complete resection can be obtained. Specific indications are listed in *Table 1*. General data in this patient category are more limited but without any doubt, surgical procedures are technically more challenging compared to interventions after SRT for early-stage lung cancer (*Figures 3,4*). There are multiple reasons for this difference. By definition, locally advanced tumors are more centrally located which provokes hilar and

mediastinal fibrosis after high-dose radiotherapy. In its turn, this fibrotic reaction renders dissection of the pulmonary artery more hazardous and often, intrapericardial control of the pulmonary vessels is required. If complications as a lung abscess or an infected cavity occur, the technical complexity of the intervention is further increased with a higher incidence of postoperative complications as empyema and bronchopleural fistula with their associated high mortality rate (44).

Compared to induction chemoradiation the applied radiation dose in chemoradiation with curative intent is higher (>59 Gy) and the interval between radiation and intervention for recurrence is usually longer than two months. Following this period the tissue response to radiation is more pronounced as demonstrated in a rat model showing that the early post-radiation phase (6 to 12 weeks) is characterized by parenchymal and vascular inflammation, whereas in the late phase (34 to 38 weeks) fibroblast hypercellularity and collagen deposition are the main features (45). Increasing the interval between radiation and operation may give rise to a more difficult identification, manipulation and dissection of tissue, therefore leading to a more tedious intervention resulting in increased blood loss compared to a standard procedure. Major procedures may be necessary with clamping of intrapericardial pulmonary vessels or chest wall resection which prolong operative time (46). Subsequently, a more protracted postoperative course may be anticipated with a higher incidence of postoperative morbidity.

Already in 2008, Bauman and colleagues reported a retrospective series of 24 consecutive patients who underwent salvage resection after definitive high-dose radiation >59 Gy for NSCLC, 22 having concurrent chemotherapy (47). In total, 25 resections were performed, mostly (bi)lobectomies and pneumonectomies. One patient died of adult respiratory distress syndrome and 14 patients experienced perioperative morbidity, 8 of them having at least one major complication. No bronchopleural fistulas were recorded probably due to extensive protection of the stump which in 19 cases was covered by a vascularized flap consisting of 16 omental flaps, 2 intercostal muscle pedicles and 1 pericardial fat pad (47). Viable tumor was present in 19 patients. Median OS was 30 months and estimated 3-year survival rate 47%.

Schreiner and colleagues recently described 9 patients who underwent salvage surgery after definitive chemoradiation for a locally advanced NSCLC with a median radiation dose of 66.2 Gy (48). Median interval

between chemoradiation and salvage surgery was 30.2 weeks. There was one postoperative death. Median OS time was 23 months, median progression-free survival 21 months, and overall 3-year survival rate 47%, similar to the results of Bauman *et al.* (47).

Shimada *et al.* reported a series of 18 patients, either with relapse or persistent tumor after a median radiotherapy dose of 60 Gy, who underwent salvage surgery (49). In 13 patients, a salvage lobectomy was performed and in 5 patients, a pneumonectomy was performed. There were no operative deaths but complications occurred in 28% of patients. Complete resection was obtained in 89% with a complete pathological response in 28%. Three-year overall and recurrence-free survival rates were 78% and 72%, respectively (49).

These reports show that salvage surgery after full-dose chemoradiation for locally advanced disease is feasible but technically more complex compared to salvage resection after SRT for peripheral, early-stage lung cancer.

Acknowledgements

None.

Footnote

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

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Cite this article as: Van Breussegem A, Hendriks JM, Lauwers P, Van Schil PE. Salvage surgery after high-dose radiotherapy. *J Thorac Dis* 2017;9(Suppl 3):S193-S200. doi: 10.21037/jtd.2017.03.88

Surgery versus stereotactic ablative radiotherapy (SABR) for early-stage non-small cell lung cancer: less is not more

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Abstract: High level evidence from randomized studies comparing surgery to stereotactic ablative radiotherapy (SABR) is lacking and available retrospective cohort and case control studies are highly variable in how thoroughly they define and stage lung cancer, in how they determine operability, and in the offered surgical approaches to operable lung cancer (open *vs.* video-assisted). This makes it difficult to compare best radiotherapy and best surgery approaches to treatment and to be confident in conclusions of equipoise between the two modalities. What has become clear from the controversy surrounding surgery versus SABR for early stage lung cancer is the desire to optimize treatment efficacy while minimizing invasiveness and morbidity. This review highlights the ongoing debate in light of these goals.

Keywords: Lobectomy; video-assisted thoracoscopic surgery (VATS); stereotactic; lung cancer

Submitted Feb 10, 2016. Accepted for publication Mar 10, 2016.

doi: [10.21037/jtd.2016.04.40](https://doi.org/10.21037/jtd.2016.04.40)

View this article at: <http://dx.doi.org/10.21037/jtd.2016.04.40>

Introduction

More than 1.8 million people are diagnosed with cancers of the lung and bronchus per year, and non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths worldwide (1). With increasing life expectancy and improvements in medical imaging, the number of affected patients is expected to escalate even further. While previous data suggested that only 25% of patients present with early-stage disease (2), the National Lung Screening Trial (NLST) (3) has confirmed that computed tomography (CT) screening leads to the detection of smaller and hence earlier stage lung cancers, resulting in a 20% mortality reduction. Standard therapy for operable, clinical stage 1 NSCLC is lobectomy with mediastinal lymph node dissection or sampling. That said, lung cancer is a disease of the elderly and a number of patients with early-stage lung cancer present with significant comorbid conditions. Tumor control in patients deemed too high risk to undergo surgery

was suboptimal in the era of conventionally fractionated radiotherapy, with 5-year overall survival rates ranging from 6–32% (4). Dose escalation studies during that time-frame demonstrated modest improvement in local control and survival, but with undesirable toxicity profiles (5). In the last decade, stereotactic ablative radiotherapy (SABR) has emerged from applications in intracranial neoplasms and was evaluated in light of its ability to provide higher doses to more precisely targeted areas in a shorter timeframe than conventional radiotherapy. Unfortunately, high level evidence from randomized studies comparing surgery to SABR is lacking and available retrospective cohort and case control studies are highly variable in how they define and stage lung cancer, determine operability, and in the offered surgical approaches to operable lung cancer (open *vs.* video-assisted). This makes it difficult to compare best radiotherapy and best surgical approaches to treatment and to be confident in conclusions of equipoise between the two modalities. What has become clear from the controversy

surrounding surgery versus SABR for early stage lung cancer is the desire to optimize treatment efficacy while minimizing invasiveness and morbidity. This review attempts to highlight the ongoing debate in light of these goals.

Pre-treatment staging

Lung cancer survival is intimately linked to stage of disease (6) and well-established guidelines from the American Association of Chest Physicians (ACCP) (2) and National Cancer Care Network (NCCN) (7) highlight the importance of both tissue diagnosis and a complete metastatic workup in all stages of NSCLC. Pursuant to that and crucial to accurate staging is a thorough evaluation of the mediastinum. CT and 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) imaging is valuable to that evaluation. However, false-negative rates of 5–15% and false-positive rates of 0 to 53% make it an imperfect tool (8), and make more invasive approaches to mediastinal staging, such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and cervical and video-assisted mediastinal lymph node sampling necessary. A large multi-institutional, prospective, randomized trial has demonstrated the importance of lymph node evaluation during the surgical treatment of NSCLC (9). Yet otherwise robust prospective studies evaluating SABR as primary therapy for both operable and inoperable early stage lung cancer have not consistently required tissue diagnosis and/or formal lymph node staging. This is despite the fact that there was a 16% incidence of occult N1 or N2 disease in the 525 patients who underwent lymph node dissection for early stage lung cancer in the randomized American College of Surgeons Oncology Group (ACOSOG) Z0030 trial (9). Even data for very small tumors (<1 cm) demonstrates an occult lymph node metastasis in 7% of patients (10). In the era of electronavigational bronchoscopy, EBUS, endoscopic ultrasound (EUS), and CT-guided biopsy, providing patients with the necessary counseling, expertise and tools to accurately diagnose and stage suspected lung cancer cannot be over-emphasized. Current and future studies designed to compare the effectiveness of surgical and non-surgical treatments of NSCLC should incorporate similar strategies in all treatment arms.

Defining operability

While the designation of operable versus inoperable

lung cancer receives great press in the literature, working definitions within the context of comparing SABR to surgery are not consistently applied. The 2013 ACCP guidelines for the preoperative evaluation of lung cancer patients suggest that potential candidates for resection with either forced expiratory volume in one minute (FEV₁) or diffusing capacity of the lung for carbon monoxide (DLCO) less than sixty percent predicted undergo an estimation of the postoperative predicted volumes. Patients with postoperative predicted FEV₁ or DLCO between 30% and 60% are at increased operative risk and further simple exercise testing (six-minute walk, stair climbing) should be considered. Data from radiation oncology literature rarely includes this specific data for patients. Likewise, not all surgical data reports information relative to the oncology community regarding performance status, such as the Eastern Oncology Group (ECOG) Performance Scale. Ideally, studies comparing surgery and SABR would incorporate morbidity data which is mutually interpretable. While algorithms and scales are valuable benchmarks, when dealing with a persistently elderly and medically frail population, nothing supplants best real-time clinical judgment. Given geographical resource and skill set variations, surgeons themselves are charged with evaluating their own limitations before offering surgery to marginal lung cancer patients, and the authors would like to emphasize that the determination of operability should always be made by a board certified thoracic surgeon.

Surgery for early stage lung cancer

Dr. Evarts Graham (St Louis) reported the first successful pneumonectomy for lung cancer using a tourniquet technique in 1933 and subsequent adaptations including lobectomy and segmentectomy came much later. In 1992, Lewis and colleagues reported 100 consecutive patients who underwent video-assisted thoracoscopic surgery (VATS), including three lobectomies with anatomic hilar dissection (11). The Lung Cancer Study Group published results of a randomized trial, in 1995 that compared a sublobar resection versus a lobectomy for early stage lung cancer (12). This demonstrated a higher rate of recurrence and associated trend toward decreased disease-free survival when comparing lobar to sublobar resection for patients with cancer. This analysis of 247 patients set the tone for lobectomy as the standard of care for non-small cell lung cancer (NSCLC) for decades to come. Of note, both wedge resection and anatomic segmentectomy were included in the

sublobar analysis for this study and the majority of patients underwent open resection. There were no statistically significant differences among the treatment groups relative to prognostic factors, morbidity or mortality. In this study however, the VATS was ill-defined and included patients with mini-thoracotomy incisions and did not exclude rib spreading. At that time, patients considered high risk for thoracotomy, due to poor cardiopulmonary reserve, were being referred for radiation therapy, even for small peripheral (T1) tumors. In this light, a multicenter trial sponsored by the Cancer and Leukemia Group B (CALGB) 9335 aimed to evaluate the role of VATS wedge resection and adjuvant radiation in treating lung cancer patients considered to be high risk for thoracotomy (13). The study found VATS to be a reasonable approach with minimal morbidity and mortality for T1 lung cancers (tumors ≤ 3 cm).

In 2002, the first multicenter prospective trial (14) to standardize VATS lobectomy and evaluate it as a viable therapy for lung cancer was opened. It enrolled 128 patients for VATS lobectomy, intentionally defined as one access incision, two or three 5 mm port incisions, and no retractor use or rib spreading. The perioperative morbidity was 7.4% and 30-day mortality was 2.7%, both comparable to standards of open thoracotomy in patients with small peripheral tumors. Prolonged air leak and perioperative arrhythmia were both decreased in the VATS group relative to historical controls, affirming assumptions that would ultimately be corroborated by others: that VATS offered a sound oncologic operation at reduced morbidity, even in high risk patients. With the advent of VATS-specific instrumentation, improved techniques for lung isolation and retraction, and newer and better video equipment, those morbidity and mortality numbers have gotten even better and studies continue to show benefit with VATS versus open surgery with respect to hospital length of stay, perioperative complications, and greater likelihood of independent home discharge compared with open lobectomy for early-stage lung cancer (15). These results are reproducible in countries outside the United States, as fewer postoperative complications and shorter length of stay were recently corroborated in a European Society of Thoracic Surgery Database project which propensity matched over 2,000 patients who underwent VATS lobectomy (16). Recent studies suggest that VATS lobectomy can be accomplished in patients with significant COPD (17) or marginal pulmonary function tests with 30-day mortalities below 1% (18). VATS segmentectomy remains an option

for patients whose lung function may not otherwise allow resection, and current randomized trials are underway to assess the oncologic equivalence of these sublobar resections (19,20) as they compare to standard lobectomy. Techniques for minimally invasive segmentectomy are well described and accomplishable in most VATS programs (21,22). Finally, the ACOSOG Z0030 trial (9), which included over 1,000 patients who underwent surgical treatment of early stage lung disease demonstrated that overall survival at 5 years was 72% for stage T1 tumors and 55% for stage T2 tumors. Local recurrence-free survival was 95% for stage T1 tumors and 91% for stage T2. As suggested by Su and colleagues in a 2014 analysis of the study, this robust, multi-institutional and meticulously verified data should serve as the benchmark against which non-surgical therapy for early stage lung cancer is compared (23).

Stereotactic ablative radiotherapy (SABR) for inoperable early stage lung cancer

Stereotactic radiotherapy for intracranial cancers has been in use since the 1950's (24). The first attempts to apply it outside of the central nervous system were pioneered in the 1990's. There are several platforms through which SABR for lung cancer is delivered. The key feature which makes SABR attractive for lung cancer therapy is the ability to deliver highly specific radiation using some form of image guidance to identify and compensate for tumor motion within the respiratory cycle. In systems where 2-D imaging is utilized, fiducial markers are placed in and around the tumor to facilitate motion of tracking throughout the treatment. Planning treatment volume (PTV) is chosen based on tumor volume and some additional margin, which varies from 2–5 mm. An advantage of SABR over conventional radiotherapy is the ability to deliver doses that would precipitate much higher rates of fibrosis and pneumonitis using conventional techniques. Enthusiasm was gained by a 2005 phase I trial of SABR and completed by Timmerman and colleagues at Indiana University (25). The trial included 47 patients with stage 1A or 1B NCSLC and concluded that pathologic diagnosis was required for accrual and patients had to be deemed inoperable by a thoracic surgeon. Local failure was defined as recurrence within the treated tumor volume only, so a recurrence within the same lobe but outside the treated area, would be considered regional recurrence. The local failure rate was 21% in this study. Overall and disease free survival were not reported, but the study was designed as a dose

Table 1 Summary of prospective studies of surgery and SABR for early-stage NSCLC

Study	Year	No. patients	5-year OS (%)	5-year DFS (%)	Local recurrence rate** (%)	Notes
ACOSOG Z0030 (Surgery)	2011	1,023			4.9	
Stage T1		578	72	77		
Stage T2		440	55	58		
RTOG	2014*					
Combined stage T1 and T2		55	40	26	23.6	
Bral <i>et al.</i>	2011					
Combined stage T1 and T2		40	NR	NR	7.5 (2 yr)	2 yr OS =56%, 2yr DFS =64%
Ricardi <i>et al.</i>	2010					
Combined stage T1 and T2		62	NR	NR	3.2 (2 yr)	35.5% had unknown histology, 3 yr OS =57.1%

*, the initial RTOG 0236 data was published in 2010 but longer-term data was presented by Timmerman *et al.* in 2014; **, defined as recurrence within the same lobe. SABR, stereotactic ablative radiotherapy; NSCLC, non-small cell lung cancer; OS, overall survival; DFS, disease free survival; RTOG, Radiation Oncology Group.

escalation study. Treatment toxicities were notable and included pneumonitis, pericardial effusion, tracheal necrosis and pneumonia. The maximum tolerated dose of radiation was determined to be 66 Gy delivered in three fractions. Because this was still considerably better than outcome data for untreated or conventional radiotherapy-treated early stage lung cancer, it sparked much interest and enthusiasm, prompting the phase II Radiation Oncology Group (RTOG) 0236 study (26). Fifty five patients were treated with SABR between 2004 and 2006 for histologically confirmed NSCLC, of which 80% were stage T1a. Inoperability was determined by a pulmonologist or a thoracic surgeon. Local failure was defined as those occurring within 1 cm of the planning target volume (1.5–2.0 cm from the gross tumor volume); however, disease free survival was reported and included separate assessments of local-regional failure (within the primary site, involved lobe, hilum, or mediastinum) and disseminated recurrence (failure beyond the local and regional sites). Three-year overall and disease-free survival were 55% and 48.3% respectively. The locoregional recurrence rate was 12.8% and 20% of patients had distant recurrence. Central tumors were excluded from this study because Timmerman and colleagues had identified the risk of treatment-related complications was higher in this cohort in a secondary analysis of the initial phase I study (27). Nearly 22% of patients had a rated Grade 3 or higher adverse event by the 90-day mark, which included reduction in PFTs, hypocalcemia, or pneumonitis

(rib fracture and chest wall pain were not reported). There were no treatment-related deaths and SABR gained rapid popularity. Several retrospective studies emerged in the radiation oncology literature reporting similar three-year overall and disease-free survival data (28–30), though the standards of histologically confirmed cancer diagnosis and surgeon-led evaluation of operability were sparsely acknowledged or reported and local and regional failure definitions inconsistent.

Stereotactic ablative radiotherapy (SABR) for operable early stage lung cancer

Table 1 highlights characteristics of randomized data (26,31,32) comparing SABR to the benchmark ACOSOG Z0030 trial (9). With increasing concerns of extrapolating retrospective data on inoperable and high-risk patients to operable patients, two prospective randomized controlled studies enrolled to evaluate surgery versus SABR in operable stage 1 NSCLC patients. Both trials closed due to poor accrual and were not designed to compare best surgical practice to SABR, as open lobectomy was the most common approach, and morbidity and mortality rates were far below accepted international norms. The STARS trial included 28 sites in the USA, China and France but only seven ultimately enrolled a total of 31 patients. In the ROSEL trial, ten centers in the Netherlands were approved and only four enrolled a total of 22 patients. Chang *et al.* attempted

analysis and interpretation of the combined data from these two studies, citing similar inclusion criteria, though no histologic cancer diagnosis was required for enrollment in the ROSEL trial, and could positively affect survival data in favor of SABR (33). Of the 58 patients analyzed, 27 were assigned to surgery and 70% of them underwent open lobectomy. The authors declared equipoise between the two treatment modalities quoting the overall and disease-free survival data that favored SABR, yet the study was not designed as a non-inferiority project and was underpowered for both of these end points. Under highlighted was the 16% locoregional recurrence rate in the SABR-treated patients and surgical complication rates much higher than accepted standards. Two additional prospective randomized trials have been designed to help ascertain which patients stand to gain the most benefit from SABR. The VALOR study: Veterans Affairs Lung cancer surgery OR stereotactic Radiotherapy in the US and the SABRTooth study in the United Kingdom will aim to compare best surgical to best SABR treatments.

Treatment efficacy

Measures of treatment efficacy when comparing SABR and surgery are subject to similar constraints of comparing pathologic to clinical data, particularly as it relates to surveying for and defining disease recurrence. Pathologic data about tumor grade, margin and receptor status, pleural and lymphovascular invasion, and induction treatment effect have proven to be objective and insightful in the treatment of patients with early-stage NSCLC. Data in surgical literature suggests a relationship between surgical resection margin and local recurrence rates (34,35). A review of over 400 patients found that patients with a 10-mm margin distance had a 45% lower local recurrence risk than those with a 5-mm distance (34). Such information is available as a consequence of surgical resection, but unavailable within the context of nonsurgical therapies, including SABR. Evidence supports adjuvant chemotherapy for the 15–20% of patients with early stage NSCLC and occult lymph node metastasis on surgical pathologic review (36), information that is simply not available for patients without specimens to review. Post-treatment surveillance PET scanning will be important, but unlikely to provide timely insight until lymph node spread has become sufficient to produce avidity in mediastinal or hilar lymph node stations, at which point it is unclear whether adjuvant chemotherapy would still offer a survival benefit. The challenge of following SABR patients

post-treatment has been studied (37). Recognition of imaging patterns and development of tools and technology to detect locoregional recurrence earlier and with better accuracy will be essential to assessing the efficacy of non-surgical therapies for lung cancer.

Discussion

Although surgery is the standard of care for early stage NSCLC, the rapid evolution of non-surgical therapies, such as SABR, has brought to light important concerns about patient selection, oncologic efficacy and treatment-related morbidity. Additionally, SABR has and will continue to have an important role to play in patients who cannot undergo or refuse surgery. Scientific and technological breakthroughs have expanded the diagnostic and therapeutic armamentarium for patients with lung cancer. The pace of innovation and discovery is promising, but must not outperform quality filtering and critical review of published data. Pathologic confirmation of disease is paramount when comparing surgical resection to SABR. In much the same way surgical survival data would have less impact if patients with hamartomas and granulomas were included, patients without confirmation of cancer should be excluded from SABR data. In the era of multidisciplinary tumor boards and clinics, electronavigational bronchoscopy, EBUS, EUS, imaged guided percutaneous biopsies, single-incision and even awake VATS lung and lymph node biopsies, it should be the exception to find patients who are unfit or unwilling to undergo tissue diagnosis and thorough mediastinal staging or restaging, not the norm. This is particularly true in light of targeted therapy and molecular sequencing advances, which necessitate at least a core of tissue for analysis. Review of current prospective randomized (most is not randomized) data as detailed in this review, highlights the need for large scale, multi-institution and multi-specialty collaborations to provide sound comparison between the standard of care and non-surgical therapies. Cost analyses will be critical to our understanding and long-term survival and quality of life data should be incorporated into well-designed clinical trials.

Conclusions

Surgical resection remains the standard of care for early-stage NSCLC. Minimally invasive approaches should be considered for all patients with operable tumors. Prospective data suggests improved morbidity and

equivalent oncologic efficacy in VATS approaches to lung cancer, even in populations considered high-risk. SABR is a safe and valuable treatment option for patients who cannot or will not undergo surgery, and operability should be determined by a board-certified thoracic surgeon. More robust data is needed before drawing conclusions about the applicability of SABR as primary therapy for patients with operable early stage NSCLC, and caution should be taken when extrapolating available data.

Acknowledgements

None.

Footnote

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

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Cite this article as: White A, Swanson SJ. Surgery versus stereotactic ablative radiotherapy (SABR) for early-stage non-small cell lung cancer: less is not more. *J Thorac Dis* 2016;8(Suppl 4):S399-S405. doi: 10.21037/jtd.2016.04.40

Stereotactic ablative body radiotherapy (SABR): an alternative to surgery in stage I-II non-small-cell cancer of the lung?

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Abstract: For decades, surgery was considered to be the only standard therapy for early-stage non-small-cell lung cancer (NSCLC). However stereotactic ablative body radiotherapy (SABR) has been used in a growing number of patients and institutions since the early 2000's. Initially this technique was intended mainly for patients who were deemed to be medically inoperable due to co-morbidities or who refused surgery, but more recently it has been applied to operable patients as well. Strict criteria for treatment planning, the use of high-technology equipment and the appropriate selection of dose based on tumor size and location are of paramount importance for a proper application of SABR. Under these conditions, SABR offers high control rates with a moderate risk of severe toxicity, quite comparable to those of modern surgery. This article reviews the basic principles of SABR, its practical aspects, the definition of biologically equivalent doses, the results in terms of tumor control, survival and toxicity and an attempt will be made to compare the results of SABR with those of surgery.

Keywords: Stereotactic ablative body radiotherapy (SABR); non-small-cell lung cancer (NSCLC); early-stage; local control; survival

Submitted Apr 21, 2015. Accepted for publication Oct 22, 2015.

doi: 10.3978/j.issn.2304-3865.2015.11.02

View this article at: <http://dx.doi.org/10.3978/j.issn.2304-3865.2015.11.02>

Introduction

In spite of the remarkable progress in the biological understanding, the pathological and clinical diagnosis and in the various treatments of non-small-cell lung cancer (NSCLC), its overall prognosis remains disappointing, even in early stages. For decades, surgery was considered to be the only standard therapy in early disease, however the 5-year survival rates after a surgical resection ranged 60% to 80% in stage I and only 40% to 50% in stage II (1). Surgery, like other curative treatments for NSCLC, including stereotactic ablative body radiotherapy (SABR), (see below) may be followed by important complications, and can even lead to a decline of quality of life (2), especially in elderly patients (3). Old age and the presence of multiple co-morbidities were, and still are, responsible for the undertreatment of early stage NSCLC in a significant proportion of patients. For example in the Netherlands,

up to the late 1990's, 32% of patients aged 75 years and older could not receive any curative local treatment for stage I NSCLC (4), but that was in an era before new treatments such as video-assisted thoracoscopic surgery (VATS), radiofrequency ablation, cryosurgery and SABR, were commonly available. However since the past decade, SABR has been more and more used in a large number of patients in a growing number of institutions. It is generally accepted that this technique represents now an alternative to surgery, under well-defined conditions, and can be administered to elderly patients and to patients with multiple co-morbidities, as reported by recent reviews (5-9). The present review is primarily intended for interested chest physicians, thoracic surgeons, medical oncologists and radiation oncologists not yet experienced in SABR, and who wish to become more familiar with this technique. In this article, the basic principles of SABR, its practical aspects, the definition of dose, and the results including tumor

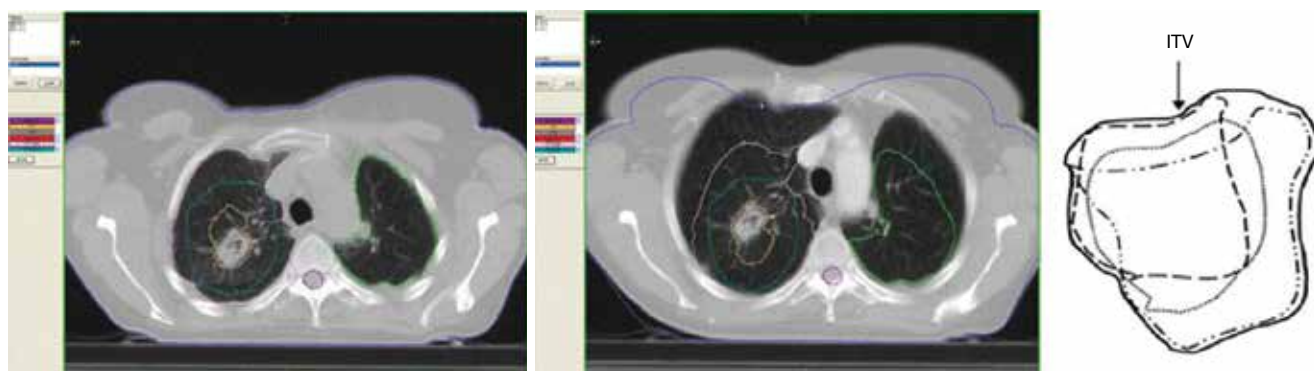


Figure 1 Schematic representation of an internal target volume (ITV) with comparative CT scans of the same patient in expiration and inspiration, and treated at our institution (CLS) (courtesy Mrs Bressan RTT, CLS).

control and toxicity will be reviewed, and an attempt will be made to compare the results of SABR with those of surgery.

Stereotactic ablative body radiotherapy (SABR)

Rationale and indications

Long before the advent of SABR (also called SBRT for stereotactic body radiotherapy), conventional radiotherapy (RT) was sometimes given to patients with early stage NSCLC who were not candidates for surgery for medical reasons or who refused surgery (10). However, conventional RT techniques had their limitations. Sixty Gy, in conventional daily fractionation of 2 Gy, represents a biologically equivalent dose (BED₁₀) of 72, which is clearly insufficient to control a NSCLC in most situations (see below). So even if some inoperable patients could be cured with conventional RT, the overall results were rather poor, with at least 40% local failures and 5-year overall survival (OS) rates of only 15-20% (10,11). Compared to conventionally fractionated RT, which for NSCLC typically delivers a dose of about 60 Gy in daily fractions of 1.8 to 2 Gy in 6 weeks, SABR represents a completely different philosophy, which delivers very high doses of highly conformal RT to relatively small volumes in a few days. This technique derives from the principles applied in intracranial stereotactic radiosurgery (SRS), which has been administered for decades for intracranial neoplasms (12), and thus uses rather similar technical tools and rather similar radiobiological principles. Thus SABR delivers very large doses, referred to by Timmerman *et al.*, as “ablative” doses (13) of RT in a few high-dose fractionation schedules, typically in 3 to 8 fractions (see below). Compared to

conventional RT, this implies major radiobiological re-considerations, referred to by Timmerman *et al.* in another paper as the “hypofractionated revolution” (14). Thus it is critical for the newcomers in the field to have a good understanding of these radiobiological principles, otherwise major problems and complications will be likely to be met. Besides this, in order to apply SABR, one needs to have at hand the most sophisticated technological tools, high competence in physics, imaging, RT planning and RT delivery, to administer safely this high, compact dose to the target. Each treatment should insure a steep gradient of dose for a maximum avoidance of normal sensitive structures, while hitting the target with the highest precision.

Target definition and treatment planning

After having confirmed the indication for SABR, the first technical step for planning SABR includes a careful identification of the target with the best currently available imaging tools, including a high-quality CT with appropriate windowing. Then, a planning 4 D CT is obtained, to define not only the gross tumor volume (GTV) and the clinical target volume (CTV), but also and most importantly the internal target volume (ITV, *Figure 1*), which represents the space occupied by the tumor during the whole respiratory cycle. Depending on the tumor volume and motion the radiation can be applied either (I) to the whole ITV, particularly in case of limited tumor volume and tumor motion, or (II) by using a “gating” technique, in which the irradiation is applied only during part of the respiratory cycle, or (III) using a “tracking” technology, in which the tumor is “followed” by the beam during the respiratory

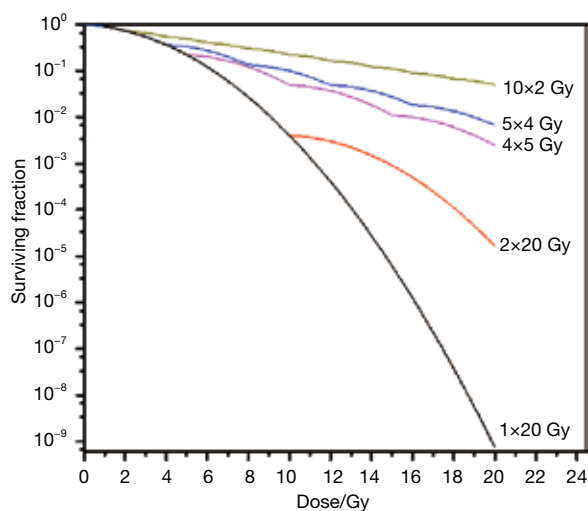


Figure 2 Cell survival curves with various fractionation schedules for a total dose of 20 Gy. Note the largely different cell kill between 20 Gy given in one fraction versus 20 Gy given in 10 fractions.

cycle. During the planning procedure, (like for any high-precision RT), it is essential to determine the best treatment plan by optimal dose-volume histograms (DVH). Normal tissue constraints values, which are defined specifically for large fractions, have to be used, and can be found in related papers (13). Although many different technical approaches have been used, to ensure the best distribution of dose high-technology linacs with intensity modulation RT (IMRT), or volumetric arc therapy (V-MAT) and image-guided RT (IGRT) technology, or other tools like the Tomotherapy or the Cyberknife systems, or even the proton-beam technology, have to be used. However at present, there are no data demonstrating the superiority of any of these treatment techniques over any other ones. Stable and reproducible positioning is essential, using either various frame systems to better immobilize the patients, or frameless systems using markers and image-guided systems.

Definition of dose in SABR

SABR implies a large total dose in a few fractions. It should be remembered that what is called a radiobiological dose has not at all the same meaning as a physical dose. Due to the decreased or absent DNA repair when large individual doses per fraction are given to any tissue (tumor or normal tissue), a dose such as 20 Gy given in one fraction is much more efficient than 20 Gy given in 10 fraction (*Figure 2*).

Table 1 Examples of five different schedules used for SABR compared with one conventional schedule of 60 Gy in 30 fractions, and their corresponding BED10 values

Total dose in Gy/number of fractions	BED10
48/4	106
45/3	113
60/30	72
60/8	105
60/5	132
60/3	180

SABR, stereotactic ablative body radiotherapy; BED, biologically equivalent dose.

Similarly, 60 Gy in 3 fractions is much more “tumoricidal” (and hugely more toxic!) than 60 Gy given in 30 fractions. Thus, to establish RT protocols with biologically equivalent doses while using different fractionation schedules, various calculation formulae can be used, like the BED equation, where (3,10):

$$BED = D(1 + d / \alpha / \beta),$$

where *BED* = biologically equivalent dose;

D = total dose in Gy;

d = dose per fraction in Gy;

α / β = coefficient for tumors or normal tissues.

Some examples of SABR schedules and one of a conventional schedule of 60 Gy in 30 fractions, and their corresponding BED10 values are displayed on *Table 1*. One can see that any dose used for SABR is largely superior to that of the conventional RT scheme. The differences are even greater when taking an α/β value of 3 (BED3) for normal tissues. Specific normal tissue tolerance-dose constraints for 1-5 fractions schedules have to be used and recommendations can be found in the literature (13). This explains why, choosing a protocol for tumors in the vicinity of sensitive normal structures, most investigators today will carefully adapt the total dose and the dose per fraction to decrease the risk of major tissue complications (see below).

Results of SABR

Local control and survival

Following SABR for stage I and II NSCLC, several endpoints should be considered to evaluate its success or failure. Local control should ideally be the most important

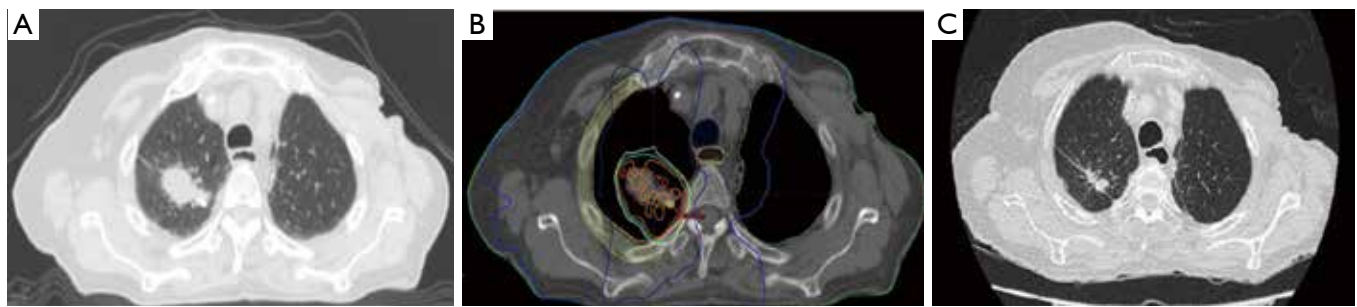


Figure 3 CT scan of a 80-year-old patient treated at our institution (CLS) for a right upper lobe NSCLC (A). He received a SABR of 60 Gy in 5 fractions with a V-MAT technique (B). CT scan at 6 months shows some residual opacity secondary to the treatment (C).

Table 2 Summary of studies on SABR for early stage non-small cell lung cancer (17-32)

Series	Year	Patients	LC	2 y S	3 y S
Onishi (17)	2004	245	85%	–	56%
Xia (18)	2006	43	81%	78%	–
Lagerwaard (19)	2007	206	81%	–	64%
Chen (20)	2008	65	88%	–	57%
Baumann (21)	2009	57	92%	–	60%
Bradley (22)	2010	91	86%	–	–
Timmerman (23)	2010	59	97%	–	56%
Ricardi (24)	2010	57	92%	–	60%
Matsuo (25)	2011	101	93%	80%	–
Widder (26)	2011	202	95%	72%	–
Takeda (27)	2012	173	80%	–	–
Shibamoto (28)	2012	180	87%	–	–
Taremi (29)	2012	108	–	63%	–
Hamamoto (30)	2012	128	87%	–	–
Crabtree (31)	2014	151	97%	–	52%
Kestin (32)	2014	483	91%	–	–

LC, local control; 2 y S: 2-year survival; 3 y S: 3-year survival.

endpoint in SABR, as it should reflect directly the efficacy of the technique, especially when compared to surgery. However the interpretation of the radiographic response is often difficult. A complete disappearance of the tumor is observed only in a minority of patients, and even in case of permanent local control one can still identify some abnormalities, even months later (*Figure 3*). In a review, 60% to 100% of patients were expected to have radiographic changes after SABR (15). The changes observed on CT could be scored into five categories: (I) diffuse consolidation, (II) patchy consolidation and ground-glass opacities (GGO), (III) diffuse GGO, (IV) patchy GGO, and (V) no evidence

of increased density (15). All these can mean permanent local control. FDG-PET may be helpful but inflammatory response may persist more than 12 months (15,16). Interestingly, late radiological changes may differ depending on the SABR technique that was used. Arc-SABR trended towards more pronounced radiological changes, with a different pattern, compared to changes seen after fixed-beams SABR (16). Overall, after SABR, permanent local control of the tumor is observed in 81% to 97% of treated patients (*Table 2*) (17-32). The next other major endpoint is survival: in the same series, survival at 3 years was reported to be between 52% and 64% (*Table 2*) (17-32). Examples

of some typical series show fairly consistent results. Onishi *et al.* have treated 245 patients in 13 Japanese institutions, with a median BED dose of 108 Gy (57-180 Gy) (17). Local progression occurred in 14.5% , and the 3-year-survival was 56%, with a cause-specific survival of 78%, indicating that a significant proportion of deaths were not cancer-related but were due to other co-morbidities (17). Lagerwaard *et al.* from VUMC, Amsterdam, have reported on 206 patients treated with 3 schedules of 3×20 Gy, 5×12 Gy and 8×7.5 Gy, depending on T stage and proximity of sensitive structures (19) (see also below). Median survival was 34 months, local failures were observed only in 3% and regional failures in 9% (19). Bradley *et al.* prospectively registered and analyzed 91 patients from Washington University School of Medicine (WUSM) in St Louis, with 3×18 Gy for peripheral tumors and 5×9 Gy for tumors in close vicinity of critical structures (22). Most patients had either a poor performance status or poor lung functions. Two-year local control was achieved in 86% of patients (22). Crabtree *et al.* have reviewed 151 SABR patients, whom they compared to 458 surgical patients (31) (see below). BED10 varied between 85.5 and 151.2. For the SABR group, 3-year local control was 89% and OS 52% (31).

Optimal dose of SBRT

Since the first reports on SABR, many different schedules of dose have been explored, in order to find the best therapeutic ratio, taking into account the best probability of tumor control with a minimal risk of causing major complications.

One initial dose-escalation phase I study was initiated at Indiana University to assess toxicity and local control rates (33). Forty-seven patients were treated with SABR escalating from a starting dose of 24 Gy in three fractions up to 72 Gy in three fractions. Patients were stratified by T stage and tumor size. The maximum tolerated dose (MTD) was 66 Gy in 3 fractions for tumors larger than 5 cm and was not reached for T1 tumors at 60 Gy in 3 fractions or tumors less than 5 cm at 66 Gy in 3 fractions (33). Chi *et al.* have extensively reviewed and linked radiobiological modeling and clinical outcome from 9 series of patients (34). Their estimates indicate a clear dose-response relationship: for example with BED10 values of 72, 84, 106 (see corresponding doses and fractions in Gray on *Table 1*), the progression-free survival at 30 months (PFS30) is only 15%, 24%, and 34%, respectively (34). With higher BED10, the PFS30 increases markedly: BED10 values of 113 and 125 correspond to a PFS30 of 95% and 99%, respectively

and then of course a plateau is reached (34). Beyond these BED10 values, one may question the necessity to administer higher RT doses, as the toxicity of normal tissues increases even more (see below). Kestin *et al.* have reviewed 505 T1 and T2 NSCLC in 483 patients treated by SABR in 5 institutions in the USA, Germany, The Netherlands and Canada (32). All were treated with on-line image-guidance RT (32). Five different schedules, with a median prescription BED10 of 132 Gy, were used. A clear dose-response relationship for local control was demonstrated, with an optimal BED10 > to 125 Gy (32). Zhang *et al.* have performed a meta-analysis on 2,587 patients from 34 observational studies (35). BED was divided into 4 dose groups: low (<83.2), medium (83.2-106), medium to high [106-146] and high (>146). As expected, overall 2- and 3-year survivals were higher in the medium dose and medium to high dose groups compared to the low dose group. However, and interestingly, the former two groups were also superior to the high dose group for OS (35). Not all studies however suggest the concept of the dose-response hypothesis in SABR. Van Baardwijk *et al.* in their systematic overview of 15 studies on SBRT (=SABR) found no correlation between the freedom from local progression and the EQD2,T, or equivalent dose in 2 Gy fractions (36). In any case, it seems clear from most studies that a BED10 beyond a certain value (around 120-130 or so) may not only be unnecessary, as one could estimate from Chi *et al.*'s data (34), but may be even detrimental, due to an increased toxicity.

Patterns of failures

As seen in *Table 2*, the rate of local control in most series is above 85%. Provided that a careful initial work up is made, to exclude nodal disease, the regional failure rate should also be low (see below). Thus the largest proportion of failures are represented by distant metastases (37). Bradley *et al.* in their series of 91 patients from WUSM, have reported that the majority of the failures were distant, with 19 of them being distant metastases, with or without some local (7 cases) and/or regional component (22). Distant failures negatively impacted the OS. In addition, 15 patients developed a second primary lung cancer (22). The largest study to date regarding the pattern of failure was published by Senti *et al.* from VUMC Amsterdam (38). They have assessed 676 patients treated by SABR between 2003 and 2011 (38). Eighteen percent had a disease recurrence, with an actuarial 2-year rate of local, regional (nodal) and distant

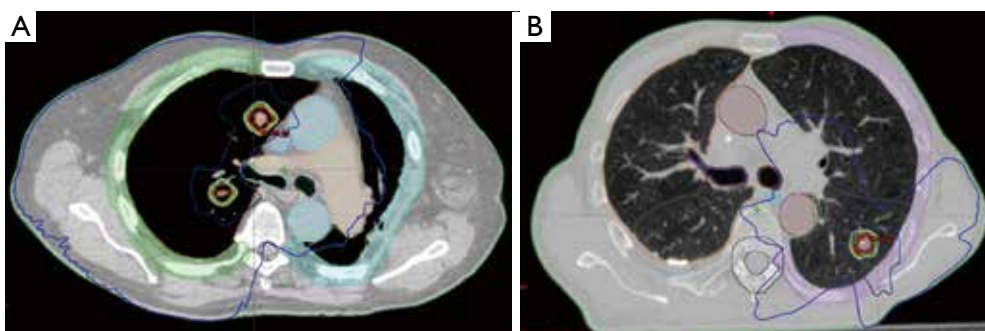


Figure 4 Example of two different patients treated at our institution (CLS) with stereotactic ablative body radiotherapy (SABR). (A) This patient received for two central lesions a dose of 60 Gy in 8 fractions of 7.5 Gy (BED10: 105); (B) the second patient received for a left upper lobe lesion a dose of 60 Gy in 5 fractions of 12 Gy (BED10: 132).

recurrence rate of 4.9%, 7.8%, and 14.7%, respectively, and with corresponding rates at 5 years of 10.5%, 12.7% and 19.9%. New pulmonary lesions, or second primary tumors, developed in 6% of all patients (38).

Toxicity

With SABR, like with high-dose, conventional RT, there is a potential risk of major complications, such as radiation pneumonitis, oesophagitis and brachial plexopathy. In addition, new severe and sometimes fatal complications have been reported with SABR, including tracheo-oesophageal fistulae, broncho-pulmonary fistulae, cardiotoxicity and chest wall necrosis (39). The latter complication, along with rib fractures, may be particularly severe and painful. Timmerman *et al.* in a seminal paper have reported their experience on 70 patients treated for T1 and T2 (<7 cm) with 60-66 Gy in 3 fractions (BED10: 180-211) (40). Significant grade 3 to 5 toxicity occurred in 14 patients, with 6 toxic deaths. Patients with peripheral lung tumors had a 2-year freedom from severe toxicity of 83% versus only 54% for centrally located tumors (40). They have defined an area referred to as the zone of the proximal bronchial tree, in which very high BED doses should be prohibited (40). In this regard, Lagerwaard *et al.* have designed a “risk-adapted” protocol taking into account tumor size and location (19). T1 peripheral tumors received 60 Gy in 3 fractions (BED10: 180), T1 with broad contact with the thoracic wall or T2 tumors received 60 Gy in 5 fractions (BED10: 132) and tumors adjacent to the heart, hilus and mediastinum received 60 Gy in 8 fractions (BED10: 105) (19). With this protocol, which reduces considerably the biological dose given to the normal “central” organs,

severe toxicity was observed only in 3% of all patients, without compromising the overall local control, which was excellent with only 3% crude local failure rate (19). *Figure 4* shows two examples of central or peripheral lesions treated at our institution (CLS), with doses adapted to their location. Senti *et al.* have reviewed the toxicity of SABR based on 20 publications including 563 central lung tumors (5). They confirm that with the above-mentioned precautions, tumor location did not impact OS or toxicity (5).

Medically operable or inoperable patients

At its beginning, SABR was intended for patients who were deemed inoperable because of age or multiple comorbidities and unacceptable surgical risks. However patients who refused surgery were also candidates for this new procedure. Onishi *et al.* in their series of 245 patients, reported that 158 were considered to be inoperable and 87 to be operable (17). There was a highly significant difference in survival ($P < 0.01$) between the two categories in favor of the operable patients, the latter having a 3-year-survival of 88%. In the group of inoperable patients, the rate of intercurrent deaths (deaths from other causes) was 19.1% versus only 3.4% for operable patients (17). This explains at least in part the large difference in OS between the two groups. Lagerwaard *et al.* found that in their prospective database of SABR, 177 patients (25% of their cases) were deemed potentially operable, using strict criteria (41). In this group of patients, the 1- and 3-year survival rates were 94.7% and 84.7%, respectively, and the local control rates 98% and 93%, respectively (41). Interestingly, in certain circumstances, a biopsy prior to SABR can be omitted. Versteegen *et al.* have analyzed a fairly large cohort

of patients, with (209 patients) or without (382) a biopsy prior to SABR (42). Local control and OS were exactly the same in the two groups of patients (42). To not biopsy certain patients is based on the fact that only 1-4% of FDG-PET positive lesions undergoing surgery are benign (42), and thus with a careful imaging assessment, the risk without a biopsy of treating a benign lesion instead of a cancerous lesion is low.

At this point the question is raised whether SBRT could be an alternative to surgery, even in the most favorable category of patients with early NSCLC.

Surgery versus SABR for stage I and II NSCLC

Evidently to compare the efficiency of SABR vis-à-vis surgery, randomized controlled trials are needed. Unfortunately, three major initiatives in the USA and Europe have failed recently, due to poor accrual (43). One has thus to rely on matched-paired analyses, in which carefully matched patients in each comparative groups are analyzed. Versteegen *et al.* have matched SABR patients and patients treated by VATS from six hospitals in The Netherlands (44). The cohort consisted of 64 SABR and 64 VATS. Post SABR local control rates were superior at 1 and 3 years (96.8% and 93%, versus 86.9% and 82.6% respectively, $P=0.04$), but distant recurrence and OS were not different (44). Crabtree *et al.* from WUSM compared 462 surgical patients to 76 receiving SABR, and found that surgical patients were healthier and had a better tumor control compared with those receiving SABR (31). However when they did a propensity analysis, they found that local recurrence and disease-specific survival were similar in the two groups (31). A meta-analysis of six studies containing 864 matched-paired patients was performed by Zhang *et al.* (45). Pooled data at 1 and 3 years indicate a better long-term OS with surgery. However the rate of cancer deaths was the same in the two groups of patients, which strongly suggests that in spite of the matching of patients, those undergoing SABR may have been less healthy than the surgical patients. This was indirectly demonstrated by the fact that there was no significant difference in cause-specific survival, disease-free survival or local control between the SABR and the surgical patients (45). Solda *et al.* have reviewed 45 reports containing 3,771 patients treated with SABR and compared them to 2,038 surgical patients (46). They found that the 2-year survival was 70% after SABR versus 68% after surgery (46). As regards performance status (PS) and comorbidity as independent prognostic

factors which may be used for treatment decisions, Louie *et al.* have constructed univariate and multivariate models to establish recursive partitioning analyses (RPA) classes and a nomogram (47). RPA identified two risk classes based on tumor diameter, age, PS and co-morbidity index, but performed poorly in surgical patients, whereas the nomogram retained a strong performance for surgery and SABR (47).

Finally, the enthusiasm generated by all the “positive” data on SBRT should be tempered by a more critical assessment of this new technique. Brada *et al.* in a recent editorial (48) have expressed a series of reservations vis-à-vis the “overconfidence” and “self-congratulation” around SABR (48). For example they remind that other newer approaches, like new surgical techniques (VATS), radiofrequency or thermal ablation may provide equivalent tumor control as SABR (48). They also underscore that the local control after SABR may be overestimated, given for example the difficulty to assess this endpoint with the current imaging means (see above), and that long-term toxicity may be underestimated as well. They question whether SABR impacts on the natural history of co-morbid situations. They also emphasize that more studies are needed to better define a series of unsolved or insufficiently solved issues, for example on respiratory and cardiac co-morbidities, on the optimal dose and fractionation and on long-term toxicities (48).

Conclusions

SABR is now a well-established technique for the treatment of early stage NSCLC, which requires a high quality of the teams and of the techniques to be used. Besides this high technology, a good understanding of the radiobiological principles is of paramount importance, in order to decrease the risk of severe complications. A dose-adapted scheme has to be used in each institution practicing SABR. Probably a BED10 dose over 120-130 is unnecessary for peripheral lesions, and should be even lower for centrally located tumors, probably not beyond 110. Results show at this point a very good local control, and an acceptable toxicity, provided a proper overall evaluation is made and the appropriate biological effective dose is selected. SABR is now a first choice for medically inoperable patients. For operable patients, at the present time, surgery remains the standard, but SABR can be a good second option for patients who refuse surgery. At the present time though,

more studies are needed because a number of problems have not been entirely solved and longer follow-ups are required.

Acknowledgements

The author would like to thank Mrs Stefania Bressan who has provided figures 1,3 and 4 in this article.

Footnote

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

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Cite this article as: Mirimanoff RO. Stereotactic ablative body radiotherapy (SABR): an alternative to surgery in stage I-II non-small-cell cancer of the lung? *Chinese Clinical Oncology* 2015;4(4):42. doi: 10.3978/j.issn.2304-3865.2015.11.02

Stereotactic ablative body radiation therapy or surgery for operable early non-small cell lung cancer patients: bound hand and foot to evidence

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Provenance: This is an invited Editorial commissioned by the Section Editor Min Zhang (The First Affiliated Hospital of Chongqing Medical University, Chongqing, China).

Comment on: Deng HY, Wang YC, Ni PZ, *et al.* Radiotherapy, lobectomy or sublobar resection? A meta-analysis of the choices for treating stage I non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2017;51:203-10.

Submitted Feb 06, 2017. Accepted for publication Feb 06, 2017.

doi: 10.21037/jtd.2017.03.25

View this article at: <http://dx.doi.org/10.21037/jtd.2017.03.25>

Surgery is the standard treatment for operable early stage (stage I: T1–T2N0M0) non-small cell lung cancer (NSCLC) patients. Lobectomy, the surgical resection of a single lobe, is generally accepted as the standard procedure, since sublobar resection has not proved to provide equivalent results yet (1). Video-assisted thoracoscopic surgery (VATS) is becoming the gold standard surgical approach compared to open thoracotomy, as there is no difference in outcomes (2,3). Importantly, a systematic lymph node dissection should be performed in all cases to ensure complete resection. The 5-year overall survival (OS) is 47–51% in patients with clinical stage IA–IB, and 58–73% in surgically staged IA–IB patients, respectively (4). The incidence of local recurrence ranged from 7–23% in large surgical retrospective studies (5,6).

Within the recent years, stereotactic ablative body radiation therapy (SABR) [or stereotactic body radiotherapy (SBRT)] has become the standard of care in non-operable early stage NSCLC patients. SABR is an external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions. Given that this technique demonstrated high local control rate (85–95%), and a low toxicity profile (7), SABR

has been experimentally proposed to a limited number of operable patients with encouraging results (8-10).

Several retrospective studies (overviews, matched-pair analyses and meta-analysis based on the literature) have tried to compare surgery and SABR with conflicting results. This is not surprising given that non-comparable patients have been included. SABR patients were generally inoperable, with higher comorbidities scores (11-14). Death, in the SABR population, is mostly due to intercurrent causes, and OS may then not be considered as a valid comparison endpoint (15). It is also likely that SABR and surgical populations itself were heterogeneous. Surgical procedures differed in reported series (wedge resection, segmentectomy, lobectomy, VATS or open surgery). Several critical factors for local control in SABR patients (mainly the tumor volume and the dose of irradiation) have been highlighted and varied widely in different protocols (16). The definition of the local relapse (within the planned target volume (PTV) or within the lobe), the prescription criteria (at the isocenter or at an encompassed isodose), and procedures for diagnosing relapses are others parameters that largely differ in series, thereby making comparisons more difficult. Finally, the absence of accurate node sampling prior to treatment in SABR patients may lead to a clinical under-staging. Retrospectives series have yet

showed that occult node metastasis can occur in 5–10% of selected stage IA NSCLC (17).

As an example, the last recently published meta-analysis by Deng *et al.* meets the previously described criteria. Selected retrospective studies integrated non-comparable (SABR *vs.* surgery) patients with mixed populations. Inoperable SABR patients had poorer conditions (older, higher comorbidities scores, and poorer respiratory tests results) than surgical patients, leading to decreased OS. Surgical and SABR technical procedures varied broadly and/or were not reported (12,18,19). In conclusion, existing retrospective data, including meta-analysis on the literature, should be interpreted with extreme caution (11-14).

There is few (mainly two small non-randomized phase II) available, but promising, prospective data on SABR in operable patients. In the Japan Clinical Oncology Group (JCOG) study 0403, SABR (48 Gy in 4 fractions) was delivered in 65/169 (38%) operable patients with histologically or cytologically proven peripheral cT1N0M0 NSCLC. The 3-year OS, progression-free survival (PFS), local PFS, and event-free survival rates were 76.5%, 68.6%, 54.5%, and 51.4%, respectively. The most frequent failure was distant metastases in 21 (33%) cases, followed by 16 (25%) regional lymph node failures (20). In the preliminary results of the Radiation Therapy Oncology Group (RTOG) 0618 phase II trial including 26 evaluable patients, the total prescribed SABR dose was 54 Gy delivered in 3 fractions. The 2-year estimates of local failure (primary tumor plus involved lobe failure), regional failure, and distant failures rates were 19.2%, 11.7%, and 15.4%, respectively (21).

Three randomized trials have failed to compare SABR to surgery in operable patients due to poor accrual (ACOSOG Z4099, ROSEL and STARS trials). Data from prematurely terminated STARS and ROSEL studies were pooled but the analysis of the included 58 patients could at best be hypothesis generating (10). New comparative randomized studies are ongoing such as POSTILV (NCT01753414), SABRtooth (NCT02629458), STABLE-MATES (NCT02468024; two later studies including borderline operable patients), and the Veterans Affairs VALOR (NCT02984761, active but not yet recruiting). Only such prospective randomized studies, including quality of life and cost analyses, will really be able to conclude if SABR should be proposed in operable early-stage NSCLC patients.

Acknowledgements

None.

Footnote

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

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Cite this article as: Levy A, Mercier O, Le Péchoux C. Stereotactic ablative body radiation therapy or surgery for operable early non-small cell lung cancer patients: bound hand and foot to evidence. *J Thorac Dis* 2017;9(3):482-484. doi: 10.21037/jtd.2017.03.25

Optimal sequencing of adjuvant chemotherapy and radiation therapy in resected non-small cell lung cancer with pathological N2 disease

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Submitted Apr 06, 2016. Accepted for publication Apr 14, 2016.

doi: 10.21037/jtd.2016.04.23

View this article at: <http://dx.doi.org/10.21037/jtd.2016.04.23>

An impressive clinical trial record exists in the investigation of the clinical benefits and risks related to the utilization of post-operative radiation therapy (PORT) in resected localized and locally-advanced non-small cell lung cancer (NSCLC). These trials generally demonstrated that local control can be improved with the application of PORT; however, the impact on overall survival was less certain. In response to this uncertainty, the PORT Meta-analysis Trialists Group published an individual patient meta-analysis on this important topic in 1998 (1). This report identified a statistically significant reduction in survival with the application of PORT to all nodal (N0–N2) groups. In the most recent update of the meta-analysis, PORT was associated with an 18% relative increase in the risk of death (i.e., hazard ratio: 1.18) (2).

The negative effect of PORT on survival was particularly pronounced in N0–N1 patient subgroup (1,2). In patients with N2 disease, there was no statistically significant reduction (or improvement) in survival, but a significant improvement in local recurrence rate (absolute 24%) was observed (1,2). Subsequent to the publication of this meta-analysis, utilization rate of PORT for resected NSCLC was substantially reduced. In a 2006 Surveillance, Epidemiology, and End Results (SEER) Program analysis, utilization of PORT for all nodal (N0, N1 and N2) declined by an absolute 4%, 32%, and 28% from 1992 (6 years before the PORT publication) to 2002 (4 years after the PORT publication) (3). It is important to note that the PORT meta-analysis has been criticized due to the use of older two-dimensional radiation techniques which may have led to additional toxicities no longer seen in a modern treatment population (4,5).

Recently, the American Society of Radiation Oncology (ASTRO) issued guidance for the indication and radiation treatment of PORT in resected NSCLC (6,7). This guideline document recommended against the routine utilization of PORT in completely resected (R0 resection) N0–1 NSCLC. However, the use of PORT in incompletely resected (i.e., R1: positive margin/microscopic residual cancer or R2: gross residual primary or nodal disease) for any N status patient was felt to be potentially appropriate to improve local control. In terms of R0 resected N2 disease, the guideline stated that the application of PORT in this patient population is reasonable in order to primarily improve local control. Specifically in relation of adjuvant chemotherapy, the guideline document recommended that PORT should be given sequentially (not concurrently) with any chemotherapy as not to interfere with standard of care treatment. The use of adjuvant chemotherapy has been shown to be associated with a 5–15% absolute improvement in overall survival (8,9). Given the lack of proven survival benefit with PORT for N2 disease, the recommendation was structured this way out of concern regarding any potential toxicity associated with concurrent treatment that could lead to treatment breaks or chemotherapy de-intensification.

Recently, multiple publication have demonstrated that there may be a small but significant survival benefit with the application of PORT for completely resected N2 disease (10-15). In 2006, Lally *et al.* described a SEER analysis where an improvement of survival was demonstrated in the N2 patient subset with a hazard ratio of 0.855 (95% confidence interval: 0.762 to 0.959, P=0.0077) (10). This finding was confirmed in a secondary analysis of the

Adjuvant Navelbine International Trialist Association (ANITA) trial in which the N2 subgroup of patients treated with adjuvant chemotherapy benefited from the addition of PORT (median survival improved to 47.4 months from 23.8 months) (11). A series of three recent National Cancer Database analyses (12-14) have all consistently shown survival benefits of adjuvant radiation for N2 NSCLC. Additionally, a fourth National Cancer Database analysis confirmed the survival benefits in N0-2 patients with incompletely resected disease (15). None of these papers specifically directly assessed the issue of sequencing of radiation treatment in terms of adjuvant chemotherapy.

Recently in the *International Journal of Radiation Oncology, Biology, and Physics*, Lee *et al.* presented an analysis entitled "Radiation Therapy-First Strategy After Surgery With or Without Adjuvant Chemotherapy in Stage IIIA-N2 Non-Small Cell Lung Cancer" (16). The objective of this manuscript was to investigate the issue of radiation sequencing as this institution has an institutional policy to deliver PORT prior to adjuvant chemotherapy. The authors argue that utilizing this sequencing approach may have clinical benefits if the overall tumor burden may be higher in the locoregional space rather than the systemic micrometastatic disease space. They hypothesized that this may improve locoregional control without significantly affecting overall survival.

This investigation retrospectively identified a total of 105 post-operative patients with stage IIIA (N2) NSCLC who received PORT first with (n=43, 41%) or without (n=62, 59%) subsequent post-operative adjuvant chemotherapy (POCT). Adjuvant radiotherapy with three dimension conformal radiotherapy techniques was delivered to a total dose of 50.4 to 60.0 Gy (at 1.8-2.0 Gy/day with potential of 66 Gy in margin positive cases). In terms of POCT, 4-6 cycles of platinum-based chemotherapy was initiated 3-4 weeks after completion of PORT in patients receiving such therapy. All patients were routinely followed according to a pre-existing schedule including chest X-rays, computed tomography and PET-CT.

In terms of the PORT prior to POCT and PORT alone groups, the authors described some differences in the two groups in terms of better performance status, higher forced expiratory volume in one second, and lower comorbidity index statistically favoring the PORT prior to POCT group. Additionally, the PORT prior to POCT was radiated to a higher mean dose (56.6 *vs.* 52.2 Gy, $P < 0.001$). There were no significant differences in locoregional failure, distant metastases or both conjoint failures between the two study

groups. However, the authors reported an improvement in 5-year survival favoring the PORT prior to POCT group (61.3% *vs.* 29.2%, $P < 0.001$). In a multivariable analysis, the addition of POCT and lack of pneumonectomy were associated with improved survival.

The authors of this report did not directly test the hypothesis of a PORT first being either equivalent or superior to a PORT last treatment strategy. They did report on the 5-year survival of the PORT prior to POCT and did compare that to historical controls to indirectly conclude that this strategy may be appropriate and can lead to optimal outcomes. Unfortunately, such comparisons are hypothesis generating at best and should not change practice patterns unless confirmed ideally with a prospective randomized controlled trial. In particular, the favorable survival may in part be due to patient selection as disclosed by the authors in their comparative analysis of the PORT prior to POCT versus PORT alone cohorts. Another significant limitation of this work was the lack of descriptive toxicity, chemotherapy de-intensification/delay data to gauge any potential deleterious effects of the PORT first approach.

Overall this study should be considered a first step in the investigation of this question. Ideally prospective data should be acquired to investigate this sequencing question to either show equivalence (or superiority) of this approach in terms of important clinical outcomes such as survival, local control, and toxicity. The European Organization for Research and Treatment of Cancer (EORTC) Lung Adjuvant Radiotherapy Trial (Lung ART) trial is an ongoing randomized trial enrolling patients with completed resected N2 NSCLC assessing adjuvant PORT versus no PORT therapy. The use of POCT as well as sequence (pre PORT or post PORT) will be a stratification variable for the clinical trial. Potentially, this trial may provide an important secondary analysis assessing this question of treatment sequencing and may be the basis of a future controlled trial if important clinical outcome differences are observed related to treatment sequence.

Acknowledgements

None.

Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Wenyong Tan (Department of Oncology, Shenzhen People's Hospital, Shenzhen, China).

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

Commentary on: Lee HW, Noh OK, Oh YT, *et al.* Radiation Therapy-First Strategy After Surgery With or Without Adjuvant Chemotherapy in Stage IIIA-N2 Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys* 2016;94:621-7.

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Cite this article as: Rodrigues G. Optimal sequencing of adjuvant chemotherapy and radiation therapy in resected non-small cell lung cancer with pathological N2 disease. *J Thorac Dis* 2016;8(6):E463-E465. doi: 10.21037/jtd.2016.04.23

Optimal sequencing of postoperative radiotherapy and chemotherapy in IIIA-N2 non-small cell lung cancer

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Submitted Apr 14, 2016. Accepted for publication Apr 21, 2016.

doi: 10.21037/jtd.2016.05.16

View this article at: <http://dx.doi.org/10.21037/jtd.2016.05.16>

Lee *et al.* questioned the optimal sequencing of postoperative radiotherapy (PORT) and postoperative chemotherapy (POCT) after surgery for patients with IIIA-N2 non-small cell lung cancer (NSCLC) which was left untested in a prospective randomized setting (1); and performed the PORT-first strategy with an institutional multidisciplinary consensus, based on their hypothesis that the PORT-first strategy possibly being more effective in locoregional control than the PORT after POCT without compromising proven overall survival benefit of POCT. Their study is a documentation of retrospective experience revealing a PORT-first strategy with POCT in eligible (43/105) and without POCT in medically (30/105) or protocolly (23/105) ineligible and refusing (8/105) patients. Lee *et al.* pointed out that their overall survival results of 40.2% was comparable with the literature (2,3) and their survival results of 61.3% in the patients with POCT was superior than previous series (2-5). Lee *et al.* deserves appreciation for drawing attention to the sequencing of adjuvant treatment in IIIA-N2 NSCLC to claim the possible benefit of PORT-first strategy.

Even after a radical resection, a high locoregional recurrence almost up to 40% was reported after adjuvant chemotherapy (4,6-9), and the common decision such as The American College of Radiology in their multidisciplinary Appropriateness Criteria was to encourage PORT for N2 NSCLC patients to improve locoregional control (10). One of the concerns in retrospective series presenting PORT such as in this manuscript is the variability of PORT target volume definition, especially in a wide range of years treated by different physicians,

such as documented by different cohorts (11,12). The objective evaluation of PORT reveals a significant survival benefit for N2 disease independent from chemotherapy, while a local regional control assistance in patients with N1 disease who do not receive chemotherapy (4,13-17). It would not be wrong to note the major problem in all older trials with deaths due to radiotherapy technical weaknesses which avoided local regional control effect turning out into a survival benefit (15). The phase 3 trial of “The Lung Adjuvant Radiotherapy (Lung ART)” enrolling N2 disease into PORT with modern and standardized techniques is expected to shed light on the gray zone in a prospective manner (12,18,19).

The role of PORT seems to traverse a long way from Lung Cancer Study Group trial in 1980 revealing important decrease in local recurrence from 41% to 3% without survival benefit in 5 years (13); to a warning to withhold PORT by Groupe d’Etude et de Traitement des Cancers Bronchiques based on high numbers of death following PORT (31% vs. 8%) (15). Trodella *et al.* on the other side randomized stage I NSCLC patients to receive PORT or not and concluded a significant disease free benefit with a trend for survival benefit (17). The subgroup analysis of ANITA, trial investigating the benefit of adjuvant vinorelbine by Douillard *et al.*, highlighted the significant survival benefit of PORT for N2 disease independent from chemotherapy in addition to survival benefit for N1 who did not receive chemotherapy (4). Besides, SEER data outlined a major survival gain for N2 patients with PORT (20). A recent meta-analysis, in stage IIIA-N2 NSCLC patients, acknowledged that modern PORT could improve the

5-year OS by 13% (21). A 2015 analysis of the National Cancer Data Base documented that PORT increased survival in pN2 patients (5). It is also evident that modern PORT claims additional survival advantage despite adjuvant chemotherapy (22).

PORT has also been discussed regarding the cohort who is gaining the benefit most; Matsuguma *et al.* claimed PORT to serve more in case of more than single station mediastinal nodal involvement (23), Saji *et al.* pointed out the poor prognostic group with less than ten nodes dissected and four or more nodes positive (24). SEER data could also document the major improvement of survival in N2 group in addition to more than 50% involvement of nodes dissected (25). Lopez Guerra *et al.* analyzed retrospective MD Anderson Cancer Center series of 1,402 stage I-III (N0-N1) NSCLC patients who did not receive PORT to define local regional risk factors and documented 9% local regional recurrence which provoked decrement in survival (26); where multivariate analysis pointed out the surgical procedure (single/multiple wedge + segmentectomy × lobectomy + bilobectomy + pneumonectomy), tumor size larger than 2.7 cm and visceral pleura invasion to be independent risk factors for local recurrence; N1, visceral pleura invasion, and lymphovascular invasion (LVI) to be independent risk factors for regional recurrence (26). As there is a common consensus for PORT in treating close/positive surgical margins or N2 nodal involvement, multidisciplinary individualized decision for PORT is required based on number and station of N1 involvement, LVI, visceral pleura invasion and extracapsular invasion (26,27). Hui *et al.* recently emphasized a subgroup of proper candidates among resected IIIA-N2 NSCLC population in whom PORT significantly improved the OS as the ones having three or more of the five factors of SI (smoking index: number of cigarettes smoked per day × number of cigarette-years) ≤400, cN2, pT3, SCC, and ≥4 positive nodes (28). Details of the cohort by Lee *et al.* needs to be analyzed for the percent of the patients who were expected to get benefit most.

There are points to be extracted from their cohort to enlighten the comparison. The ratio of patients staged with PET-CT before surgery would be helpful hint to understand the cohort treated; besides the follow up of the patients treated in this cohort seems a little loose to be able to capture locoregional and systemic failure with simple chest radiography or chest CT or optional annual PET-CT. As the types of surgical resection were detailed as lobectomy & bilobectomy or pneumonectomy in their patients,

quantification of regional lymph node involvement have not been detailed in this paper to reveal the patients' risk load. As the authors mentioned that no routine preoperative pathological evaluation for mediastinal disease performed and surgical resection decision was based on clinically N0-1 or single station minimal N2 disease, surgical data whether the dissection was formal or selective and postoperative data for the number of dissected nodes, positive N1 nodes/station and positive N2 nodes/stations were lacking in the manuscript. Besides, it would be great to know the related pathological details of the cohort to reveal the accurate R0 complete resection rates in both treatments (29), not only microscopically confirmed free resection margins, but also a systematic nodal dissection and the ratio of extracapsular tumor extension in nodes removed. All the patients except two were defined as clear surgical margins and though there was an enormous difference (2 patients with positive margins, one on each arm; and 101 negative margin patients, 42 on PORT-first plus POCT and 61 PORT alone), the authors analyzed the resection status both univariately and multivariately, instead of excluding these two patients.

As duration between the surgery and initiation date of POCT seemed to impact survival in colorectal and breast cancer patients, one of the most important questions about timing of PORT is whether postponing POCT might affect survival. In other tumor sites such as head and neck or breast cancer, the delay to initiate PORT has been presented to have a negative impact on outcome (30-33), while the data for lung cancer for this correlation is not reported much (34,35). A recent Canadian data documented 1,032 cases treated with POCT with a median time to adjuvant chemotherapy (TTAC) of 8 weeks where 35% of the cohort received POCT more than 10 weeks after surgery. Booth *et al.* have appreciated no association between TTAC and overall survival (OR =1.00, 95% CI =0.99-1.00) (36). In the lack of prospective data to clarify the TTAC, data by Lee *et al.* could also be defined as another cohort, though there is not a direct comparison, to point out the mild delay for POCT might not cause any sacrifice in overall survival.

The histology might have an influence on locoregional failure as adenocarcinoma and squamous cell carcinoma, due to the fact that squamous cell was pointed out to be a poor prognostic factor for survival (37); however the prognostic significance of the histology is yet to be defined in fully resected pN2 NSCLC (2). As the histology seemed to be evenly distributed here for both PORT & POCT and POCT alone groups, histology might not affect the

outcome in this cohort.

As a summary, optimal sequencing of PORT and POCT after surgery for patients with IIIA-N2 NSCLC is a candidate topic to be discussed and studied prospectively, however for now, PORT-first strategy sounds to be feasible and triggering related research where Lee *et al.* provided a first-hand retrospective valuable information to initiate the discussion.

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Wenyong Tan (Department of Oncology, Shenzhen People's Hospital, Shenzhen, China).

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

Comment on: Lee HW, Noh OK, Oh YT, *et al.* Radiation Therapy-First Strategy After Surgery With or Without Adjuvant Chemotherapy in Stage IIIA-N2 Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys* 2016;94:621-7.

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Cite this article as: Selekt U, Chang JY. Optimal sequencing of postoperative radiotherapy and chemotherapy in IIIA-N2 non-small cell lung cancer. *J Thorac Dis* 2016;8(7):1394-1397. doi: 10.21037/jtd.2016.05.16

Neoadjuvant chemoradiotherapy followed by surgery for stage IIIa and IIIb non-small-cell lung cancer (NSCLC): is it still justified?

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Abstract: For stage III non-small-cell lung cancer (NSCLC), overall survival after surgery alone is quite poor, in the range of 5% to 10% at five years, mainly due to the high incidence of local and distant failures. Randomized trials and meta-analyses have shown a modest improvement in survival with neo-adjuvant chemotherapy, however the local and distant failure rates remain high. Numerous retrospective studies and phase II trials have been published on the potential added value of radiotherapy in the neoadjuvant setting and are reviewed here. These studies have shown that the addition of radiotherapy to chemotherapy is followed by a high rate of complete resection, an encouraging rate of complete pathologic response, a high mediastinal clearance in case of N2 disease, all of which represent potential surrogates for survival. Until recently, only small randomized trials have compared neoadjuvant chemoradiation to neoadjuvant chemotherapy, and were not contributory. The recently published Swiss cooperative group (SAKK) phase III randomized trial is the only one to have accrued a sufficient number of patients for interpretation. It showed a superiority of neoadjuvant chemoradiation over neoadjuvant chemotherapy regarding overall response rate, complete resection rate and local control, with no increased haematologic toxicity or post-operative deaths. However there was no difference in the event-free survival (the primary endpoint) nor in overall survival between the two arms. Following the results of this trial, opposite opinions have been expressed regarding the possible causes of failures of this trial, and on the future role or not of radiotherapy associated with neoadjuvant chemotherapy before surgery. It is suggested that under certain conditions, in which the risk of local failures is quite high after surgery, studies on the role of neoadjuvant chemoradiation should be pursued, using novel radiotherapy techniques and schemes, and novel systemic treatments associated with radiotherapy.

Keywords: Neoadjuvant; radiotherapy; chemotherapy; surgery; non-small-cell lung cancer (NSCLC)

Submitted Dec 10, 2015. Accepted for publication Dec 21, 2015.

doi: 10.3978/j.issn.2304-3865.2015.12.05

View this article at: <http://dx.doi.org/10.3978/j.issn.2304-3865.2015.12.05>

Introduction

Neo-adjuvant or preoperative therapy for operable non-small-cell lung cancer (NSCLC) has been the subject of a large number of studies in the literature, and in spite of progress demonstrated by well conceived and well conducted phase III randomized trials and meta-analyses, many issues remain unsolved as of today, especially in locally advanced (LA) stages. In operable stage III NSCLC, there is still a considerable debate regarding the best strategy, which can include surgery followed by chemotherapy

with or without radiotherapy, neo-adjuvant chemotherapy followed by surgery with or without post-operative radiotherapy, neo-adjuvant chemoradiation followed by surgery, comprehensive chemoradiation without surgery, preceded or not by neo-adjuvant chemotherapy, and several other strategies (1,2). Neo-adjuvant treatments are aimed at improving the overall outcome of LA NSCLC by decreasing the rate of local failures and distant metastases observed after surgery alone.

After a brief reminder on the role of neo-adjuvant chemotherapy in NSCLC, this article will focus in more

details on the potential added value of radiotherapy in the neoadjuvant setting.

Neoadjuvant chemotherapy in LA NSCLC

In non-metastatic NSCLC surgery still represents the mainstay of curative treatments from stage IA to IIIA and even for part of stage IIIB. However, especially in LA NSCLC, overall survival after surgery alone remains poor, in the range of 5–10% at 5 years (3). The domain of neoadjuvant or adjuvant chemotherapy spans from stage IB to part of stage IIIB (4–8), due to the subsequent high risk of distant metastases after surgery alone.

The recent meta-analysis on neo-adjuvant chemotherapy for NSCLC has collected individual participant data from 2,385 patients included in 15 controlled randomized trials (4). Patients were centrally analyzed, and the primary outcome was overall survival. The results showed a 13% reduction in the relative risk of death, with an absolute survival improvement of 5% at 5 years, from 40% to 45% (4). In this meta-analysis, stage did not seem to alter the effect of chemotherapy. Looking at the first events, local recurrence occurred in 24%, distant recurrence in 31% and both local and distant recurrence in 9%. Altogether 33% of first events included a local failure (4). In a previous meta-analysis, which was not based on individual patient's data, the positive effect of chemotherapy was also observed, and looking specifically at 8 studies on stage III, the improvement in overall survival with chemotherapy remained statistically significant (5). However neo-adjuvant chemotherapy alone in stage III may not be sufficient, since even with this approach, the pathological complete response (pCR) rate was low, and the local-regional recurrence rate was high. For example, in three randomized trials comparing neo-adjuvant chemotherapy followed by surgery to surgery alone in stage III NSCLC, the complete pCR in the induction arm was only between 6% and 10.5% (6–8). As pCR is an indicator of response and a possible surrogate for survival (see below), it seems logical to improve pCR by an additional local treatment to surgery such as radiation therapy. In a phase II trial of the Swiss cooperative group (SAKK), in which patients received neo-adjuvant docetaxel and cisplatin for stage IIIA NSCLC, there was a good correlation between pathological response and resectability; in addition, resectability and mediastinal clearance were strongly prognostic for survival, whereas patients with no mediastinal clearing and/or an incomplete resection did poorly (9). A subsequent analysis of this phase II revealed that at 5-year

follow-up, as many as 60% of patients suffered from a local relapse (10). For these different reasons, it appears that the addition of radiotherapy to chemotherapy in neo-adjuvant strategies deserves to be strongly considered.

Neoadjuvant radiochemotherapy in LA NSCLC: retrospective studies, database and phase II trials

Retrospective studies

A large number of retrospective studies on neo-adjuvant radiochemotherapy for stage III NSCLC have been published. The overall results of a selection of eight of these are briefly discussed here (11–18). They represent altogether a total of about 1,100 patients with operable stage IIIA and IIIB (11–18). In the majority, chemotherapy consisted of cisplatin doublets, with a few carboplatin doublets, and the radiotherapy schedules were mainly conventional fractionation schemes with a few hyperfractionated schemes, with doses between 43 and 60 Gy. The pCR, when reported, varied between 16% and 27% (11,13–15,18), except in one study where it was as high as 40% (17). The median survival was between 21 and 36 months, and the 5-year overall survival between 31% and 40% (11–18). In several reports, a pCR was associated with an increased survival (11,12,17,18), and a mediastinal downstaging and/or pathological clearing was also heralding a superior outcome (12–14,16,17). Evidently, results from these retrospective studies are to be interpreted with caution due to patients' selection and other bias. However some striking results, like the rates of pCR and the relationship between pCR, downstaging and survival are encouraging and may be hypothesis-forming for prospective randomized trials.

Results of the American National Cancer Database (NCDB)

A cohort of 11,242 patients included in the NCDB, treated from 1998 to 2004 for stage IIIA (N2) NSCLC were analyzed according to the 5 following treatment categories: neoadjuvant chemoradiation followed by a lobectomy, neo-adjuvant chemoradiation followed by pneumonectomy, lobectomy followed by adjuvant treatment, pneumonectomy followed by adjuvant treatment, or concomitant chemoradiation without surgery (19). Adjuvant treatments consisted of either chemotherapy alone, radiotherapy alone, or chemoradiation following surgery. Five-year overall survival was 33.5%, 20.7%, 20.3%, 13.3%, and 10.9%, respectively for the five treatment categories (19).

Table 1 Overall results of 7 phase II, one-arm trials of neoadjuvant chemoradiotherapy for non-small-cell lung cancer

Study (reference)	Stage IIIA/IIIB (%)	Patient's number	CXT	RT (Gy)	Resection rate (%)	Operative mortality (%)	pCR (%)	Median survival (months)	3-y survival (%)	5-y survival (%)
Albain <i>et al.</i> (21)	60/40	126	[1]	Conc 45	80–85	7	21	13–17	24–27	NR
Ichinose <i>et al.</i> (22)	0/100	27	[2]	Conc 40	93	4	19	NR	56	NR
Edelman <i>et al.</i> (23)	70/30	47	[3]	Conc HF 69.6	62	0	28	29.6	64	NR
D'Angellilo <i>et al.</i> (24)	58/42	50	[4]	Conc 50.4	82	8	26	21.8	40.2	NR
Stupp <i>et al.</i> (25)	0/100	46	[5]	Sequ AF 44	76	6	13	29	47	40
Friedel <i>et al.</i> (26)	25/75	120	[6]	Conc AF 45	75	5	NR	19	NR	21.7
Eberhardt <i>et al.</i> (27)	39/61	64	[7]	Conc AF 45	89		44			26 (10 year)

CXT, types of chemotherapy: (I) cisplatin plus etoposide; (II) cisplatin plus tegafur; (III) carboplatin plus vinorelbine; (IV) cisplatin and gemcitabine; (V) cisplatin plus docetaxel; (VI) carboplatin and docetaxel; (VII) cisplatin and paclitaxel; and (VIII) cisplatin and etoposide. RT, radiotherapy schedules; Conc, concomitant chemoradiotherapy; Sequ, sequential chemoradiotherapy; HF, hyperfractionated radiotherapy; AF, accelerated fractionation radiotherapy; pCR, complete pathologic response; NR, not reported.

On multivariate analysis, the hazard ratio (HR) in favor of the neo-adjuvant chemoradiation treatment was 0.51 (CI: 0.45–0.58) (19). Of note however, no neo-adjuvant chemotherapy alone category was described in this report. A more recent study from the NCDB analyzed 1,076 patients with stage IIIA (N2) NSCLC, treated between 2003 to 2005, either with neo-adjuvant chemoradiation followed by surgery or neoadjuvant chemotherapy followed by surgery (20). Outcomes included overall survival, residual nodal disease, any adverse pathologic features, and 30-day postoperative mortality. The 5-year overall survival for the entire cohort was 39%, namely 39.2% for the neo-adjuvant chemoradiation category *vs.* 38.6% for the neo-adjuvant chemotherapy (P=NS). On multivariate analysis, neo-adjuvant chemoradiation was associated with an improved pathological outcome (20).

Phase II trials

Results of 7 selected prospective one-arm phase II studies are presented on *Table 1* (21–27). In 5 of these trials, there was a mixture of stage IIIA and IIIB, whereas 2 have included stage IIIB only (22,25). In all studies, chemotherapy consisted of cisplatin doublets or carboplatin doublets. All trials but one (25) included a concomitant chemoradiotherapy regimen, and radiotherapy schedules delivered doses between 40 and 50.4 Gy, except for one in which a hyperfractionated scheme of 69.6 Gy was administered (23). Surgical results showed a resectability rate between 62% and 93%, with a post-operative mortality between 0% and 8%. pCR, looking

at the surgical specimen of the primary tumor, was reported to be between 13% and 44%. Median survival was between 13 and 29.6 months, and 3-year survival between 24% and 64%. When overall survivals of stage IIIA and IIIB were compared, there was no difference (21,26). This most likely reflected a favorable selection of operable stage IIIB patients, but at the same time it indicated that at least a subset of stage IIIB patients could benefit from neoadjuvant chemoradiation (21,22,25,26). Finally, when reported, there was a strong correlation between complete resection (R0) and survival (25,26), mediastinal clearing and survival (21,24,25), and pCR and survival (24,25).

Surrogates for survival

From a number of retrospective studies and prospective phase II studies mentioned above, it appears thus that pCR, mediastinal downstaging or clearing, and R0 resection were associated with an improved survival. It should be reminded that after neoadjuvant chemotherapy alone, pCR was between 6% and 10% only in stage III, whereas it was between 16% and up to 40% in retrospective neo-adjuvant chemoradiation studies, and between 13% and 44% in phase II prospective neoadjuvant chemoradiation trials. Radiotherapy has not only the potential to improve pCR of the primary tumor, but to increase mediastinal clearing in case of N2 disease and to ameliorate the R0 resection rate. Yet its impact on survival would have to be demonstrated by phase III randomized trials only.

Neoadjuvant radiochemotherapy in LA NSCLC: prospective randomized trials

Neo-adjuvant chemoradiation followed by surgery versus neo-adjuvant chemotherapy followed by surgery and post-operative radiotherapy: the German phase III randomized German Lung Cancer Cooperative Group (GLCCG) trial (28)

The GLCCG in a large phase III trial has randomized 558 patients with stage IIIA and IIIB NSCLC into two treatment groups (28). The intervention group received three cycles of cisplatin and etoposide, followed by twice daily radiation to 45 Gy and concurrent carboplatin and vindesine, followed by surgical resection. The control group received three cycles of cisplatin and etoposide, followed by surgery, followed by postoperative radiotherapy to 54–68 Gy. Primary endpoint was progression-free survival and secondary endpoints were overall survival and resectability. Results showed no significant difference in progression-free survival (37% *vs.* 33%) and no difference in overall survival (39% *vs.* 31%) between the two groups (28). However the group with preoperative chemoradiation showed a better pathological response, defined here as >90% tumor clearing, with 60% *vs.* 20% ($P=0.0001$), and a better mediastinal downstaging, with 46% *vs.* 29% ($P=0.002$), with no difference in the occurrence of treatment-related deaths (6.4% *vs.* 5.7%) (28).

Thus, this important trial could clearly demonstrate a greater local efficacy of chemoradiation compared to chemotherapy alone, but there was no impact on progression-free survival and overall survival. It may be that in the control group (neo-adjuvant chemotherapy alone), the systematic use post-operative radiotherapy may have «blurred» the impact of neo-adjuvant radiotherapy of the other arm. In any case, and unfortunately, this trial did not answer the question whether the addition of radiotherapy to chemotherapy in the neo-adjuvant setting improves or not the overall outcome.

Neo-adjuvant chemoradiation followed by surgery versus neo-adjuvant chemotherapy: phase II randomized (29) and incomplete phase III randomized trials (30)

A French phase II randomized study on 47 patients with stage IIIA N2 NSCLC aimed at comparing standard induction chemotherapy (arm A: cisplatin and gemcitabine), with 2 different induction chemoradiation regimens (arm B: cisplatin and vinorelbine) and radiotherapy dose: 46 Gy, arm C: carboplatin and paclitaxel and radiotherapy dose

46 Gy (29). Response rate was higher in the 2 chemoradiation arms compared to the chemotherapy only arm (87% *vs.* 57%, $P=0.049$). Feasibility rate was the same in the 3 arms, the overall survival for the entire cohort was 43% at 3 years, with no difference between the 3 arms (29). Neither the study design nor the small number of patients could allow to evaluate a possible difference in overall survival.

A Japanese phase III randomized trial for stage IIIA N2 NSCLC was sought to ascertain whether induction concurrent chemoradiation followed by surgery could improve survival compared to induction chemotherapy followed by surgery (30). Patients received either carboplatin and docetaxel plus concurrent radiation therapy to 40 Gy followed by surgery, or induction chemotherapy alone followed by surgery (30). The study had to be stopped because of slow accrual, but 60 patients could finally be randomized. Treatments were well tolerated and there was no toxic deaths. Combined chemoradiation conferred a better local control, however there was no differences in progression-free survival or overall survival when radiotherapy was added to chemotherapy (30).

Thus these two small randomized trials showed clearly a greater measurable therapeutic effect of neoadjuvant chemoradiation compared to adjuvant chemotherapy alone, but were unable to demonstrate any impact on progression-free survival or overall survival, and this was, possibly in part, due to the small numbers of patients.

Neo-adjuvant chemoradiation followed by surgery versus neo-adjuvant chemotherapy: the Swiss phase III randomized SAKK trial (31)

The Swiss cooperative group, the SAKK, in a phase III randomized trial has enrolled 232 patients with stage IIIA N2 NSCLC into two treatment groups (31). At this time, it is the only fully completed phase III randomized trial with this design. The radiochemotherapy group (117 patients) received three cycles of neoadjuvant cisplatin and docetaxel, followed by radiotherapy with 44 Gy in 22 fractions over 3 weeks. The control group (115 patients) received the same chemotherapy alone, and all patients were scheduled to undergo surgery. Primary endpoint was event-free survival. Overall tumor response rate was 61% after chemoradiation, *vs.* 44% after chemotherapy alone ($P=0.012$). Overall, chemotherapy-related effects were moderate and similar in the two groups, and radiotherapy-related toxic effects were also moderate with 9 grade 3 events (31). Eighty five percent in the chemoradiotherapy group and 82% in the

chemotherapy group underwent surgery. A R0 resection was performed in 91% and 81%, respectively ($P=0.06$). In the 30 days after surgery, 3 patients in the chemotherapy group died, compared with none in the chemoradiotherapy group. Nodal downstaging (to N1 or N0) was observed in 64% and 53%, respectively, and the pCR in 16% and 12%, respectively in the chemoradiation group and chemotherapy only group ($P=NS$). The first event was death in 13% patients in the chemoradiation group *vs.* 8% in the chemotherapy group, and was local progression in 15% and 28%, respectively. The median event-free survival was 12.8 months in the chemoradiotherapy group and 11.6 months in the chemotherapy group ($P=0.67$). Median overall survival was 37.1 months in the chemoradiotherapy group, and 26.2 months in the chemotherapy group, but survivals at 2, 3 and 4 years were identical in the 2 treatment arms (31).

Thus, this study showed that patients who received chemoradiotherapy before surgery had an objective response, a pCR, a R0 resection rate and a mediastinal downstaging more frequently and less local progression than patients in the chemotherapy alone group. In spite of all of these, the addition of radiotherapy did neither improve event-free survival (the primary endpoint) nor overall survival (31). The reasons for this may have been due to several factors. Firstly radiotherapy was given sequentially to chemotherapy, and not concomitantly, whereas concomitant chemoradiation was shown in the NSCLC Collaborative Group meta-analysis to be superior to sequential schedules in LA disease (32). Secondly the radiotherapy dose (44 Gy), although given in a slightly accelerated schedule (equivalent to 48–50 Gy in conventional daily fractions of 2 Gy), may have been insufficient. These two factors may explain a pCR of 16%, which is inferior to the pCR rates observed in retrospective data and in phase II trials using concomitant schedules and/or higher RT doses (see *Table 1*). Other factors, including the high distant failure rates in both arms (37% and 33% rates of first relapse), the patients' selection and the relatively small number of patients may have contributed. On the other hand, the addition of radiotherapy was well tolerated and did neither increase hematological toxicity nor post-operative mortality, which were altogether low in this trial.

Discussion

Although results from retrospective data and from phase II trials have suggested that the addition of neo-adjuvant

radiotherapy to chemotherapy could improve the outcome of operable stage III NSCLC, none of the small randomized trials, including the recent SAKK trial could demonstrate any advantage in event-free, progression-free or overall survival (29-31). Does it mean that radiotherapy should be banned from the adjuvant setting in the future? At the present time, different opinions prevail:

- (I) Pless *et al.* in the conclusion of their SAKK trial, have argued that in stage III NSCLC, three modalities are not superior to two modalities, and that one local treatment may be enough (31). The main reasons were that on one hand, neoadjuvant chemotherapy alone gave similar results as neoadjuvant chemoradiation in the three published randomized trials (29-31), and that on the other hand three other large randomized trials have shown that after neoadjuvant chemotherapy, either high-dose radiotherapy alone or surgery alone were equivalent in terms of overall survival (33-35);
- (II) Eberhardt and Stuschke in an editorial commenting the results of the SAKK trial, consider that for most patients, the combination of chemotherapy and concurrent radiotherapy represents an acceptable standard (2). One of their arguments is based on their own data on intensive neoadjuvant concurrent chemoradiotherapy in which they found fairly high rates of pCR, between 30% and 40% (27,35), which were substantially higher than the 16% pCR of the SAKK study (31). They also stress that stage III disease is heterogeneous in terms of tumor volume and bulk, lymphogenic spread and co-morbidity (2). Thus, different subgroups of stage III may deserve different strategies, and personalized treatments based on co-morbidities might be a better solution (2).

Indeed, as almost all studies have shown better results with chemoradiation concerning response rate, pathological response, mediastinal clearing and local control of the disease, all of which being potential surrogates for survival, it seems justified to pursue the study of the role of concomitant chemoradiotherapy in the neoadjuvant setting, however only under certain conditions.

- (I) Better selection of patients: one should first identify subgroups of operable stage III NSCLC who probably do not need additional RT, for example stage IIIA with minimal N2 disease, and exclude this group from radiochemotherapy trials. New trials should then be dedicated to subgroups with a higher risk of local failure, such as stage

III-N2 bulky disease, stage IIIB, and superior sulcus tumors. In the latter situation in particular, neoadjuvant chemoradiation gave excellent results in phase 2 studies (36,37);

- (II) Better radiotherapy: new trials should include innovative, high-technology radiotherapy capable of delivering safely high doses of radiation, concomitantly (and not sequentially) to chemotherapy. Techniques using intensity modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT) (17), and/or adaptive radiotherapy would be essential, and schedules like accelerated fractionation (26,27), concomitant boost (35), dose-escalation or hypofractionated schemes should be worth studying;
- (III) Better systemic treatments in combination with radiotherapy: it should be remembered that current “standard” cisplatin doublets have their limitations. The pCR and local control with currently available chemotherapy alone is low, and the rate of distant failures is still high (vide supra), indicating a limited efficacy even on microscopic disease.

In conclusion, neoadjuvant chemoradiotherapy for stage III NSCLC is safe and efficient, with higher overall clinical response, higher pCR rates and a higher mediastinal clearing compared to neoadjuvant chemotherapy alone. Contrary to previous fears, radiotherapy does not add a higher toxicity nor does it increase post-operative mortality compared to chemotherapy alone. Numerous phase II trials have shown encouraging survival rates, up to 30–40% at 5 years. On the other hand, the yet available randomized studies have failed to demonstrate any advantage of adding radiotherapy in the neoadjuvant setting regarding progression-free survival or overall survival. Admittedly the number of patients enrolled was modest. Still the controversy is not being solved and further trials taking into account a better patients’ selection, innovative radiotherapy and more efficient systemic treatments need to be undertaken.

Acknowledgements

None.

Footnote

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

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Cite this article as: Mirimanoff RO. Neoadjuvant chemoradiotherapy followed by surgery for stage IIIa and IIIb non-small-cell lung cancer (NSCLC): is it still justified? *Chin Clin Oncol* 2015;4(4):49. doi: 10.3978/j.issn.2304-3865.2015.12.05

Vol 9, No 6 June 2017

ISSN 2072-1439

JOURNAL of THORACIC DISEASE

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Journal of Thoracic Disease
Volume 9 Number 6 June 2017 Pages 1439-1743 5540-5500



The Official Publication of



Print ISSN 2218-6751
Online ISSN 2226-4477

TRANSLATIONAL LUNG CANCER RESEARCH

Official publication of Society for Translational Cancer Research (STCR)
Endorsed by the Spanish Lung Cancer Group (SLCG)
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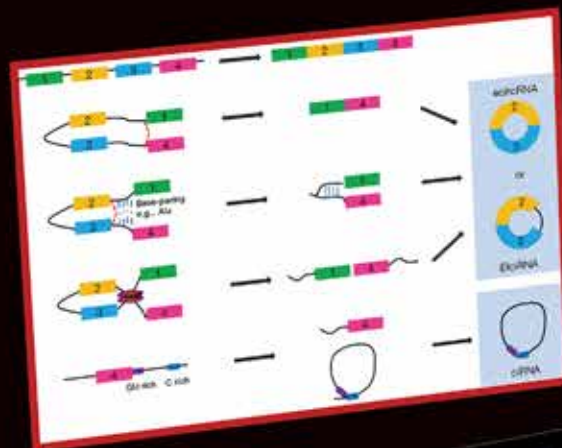
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TRANSLATIONAL CANCER RESEARCH

ISSN 2218-676X
VOL. 6, NO. 4
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Print ISSN 2305-5839
Online ISSN 2305-5847
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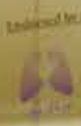
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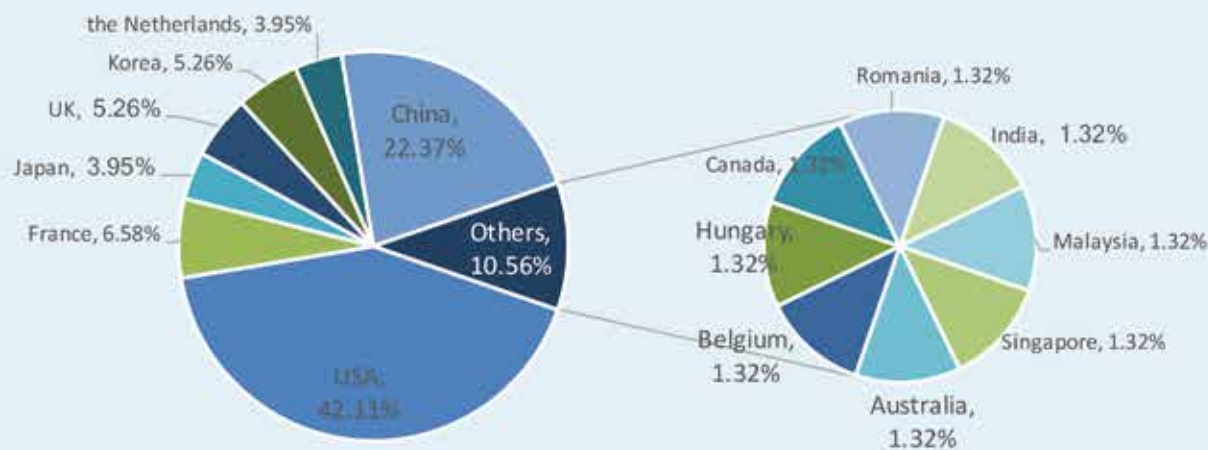
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