AME Medical Review 001

Surgery versus Stereotactic Body Radiation Therapy for Early-Stage Lung Cancer

AME Publishing Company

ASVIDE AME Surgical Video Database

www.amegroups.com

Surgery versus Stereotactic Body Radiation Therapy for Early-Stage Lung Cancer

Editors: Yaxing Shen, Zhirui Zhou

AME Publishing Company

ASVIDE AME Surgical Video Database

AME Publishing Company

Room 604 6/F Hollywood Center, 77-91 Queen's road, Sheung Wan, Hong Kong

Information on this title: http://www.amegroups.com/
For more information, contact info@amepc.org

First published 2016
Printed in China by AME Publishing Company

Editors: Yaxing Shen, Zhirui Zhou
Surgery versus Stereotactic Body Radiation Therapy for Early-Stage Lung Cancer
ISBN: 978-988-14028-4-4 Hardback

Will scholarly journals perish?

Will scholarly journals perish? This is a question that has puzzled me for years.

The introduction of online journals results in the inevitable recession of print journals. The uprise of the open access journals has been changing the structure of scholarly journals ceaselessly. What keeps me thinking is the open access of clinical trials data. What would be the bigger picture if open access to clinical trials data becomes the mainstream?

It is interesting that with the primary bottleneck lying in the availability of open data, the Big-data Clinical Trial (BCT) seems to stay where it was in spite of the increasingly popularity of "Big Data" among scientists. It has to be the fact that without open data, a statistical analysis is restricted to a particular area (or several areas). Even with big enough data, the study can only be termed as "research with big data sets" rather than "big data research", which are totally different concepts. Big Data is constituted by a plurality of dimensions. On one hand, for an individual (e.g., a patient), the relevant data covering his/her disease course is big enough; on the other hand, for the entire population, as more as individuals (e.g., patients) are expected to be included, to contains all the elements just like the "universe set" in set theory; by doing so, scientists expect to carry out the so-called clinical studies in real-world settings.

Why do the real-world-based clinical trials so appealing? It is understandable that the results and conclusions are likely to be altered in studies targeting the same issue using the same research method with sample size changed. In addition, the probability of such a "likely" is quite high. In many top journals, it is a common phenomenon that some authors tend to validate the results of one study in another population using the same research method. However, if the results are "validated" in one population, it only means that they are "repeatable". Will the results also be repeatable in the second, third, and more populations? If the attempts are not continuing, which should be, the "validation" is equivalent to "self-deception" in a sense.

When clinical research data is open accessed, we can easily integrate data from multiple centers for statistical analysis and meanwhile "validate" the results in multiple populations. If this is the case, then another question arise: can everyone easily publish his/her results/papers in high-profile journals such as the *New England Journal of Medicine*? My answer is NO.

When the open access to clinical research data becomes mainstream, we can easily find the constant update of database on the Internet. Simply by clicking on a button, we obtain the statistical results of the most current data. A further button click would display the validation results based on a specific population. The database would be updated at a certain period of time (e.g., 1 month or 1 day), and the statistical results would "likely" also be changed accordingly. At that time, the questions may change to "would any researchers publish their findings in a journal?" Well, even if someone is still keen to write such articles, journals may be reluctant to publish them because of the indefiniteness of the findings with the risk of being overturned at anytime.

Eventually here it comes the serious question: will scholarly journals perish? My answer is still NO. Then in what way the scholarly journals would probably lead to?

During my Business Administration course, my teacher distributed to us an article from the Case Study column of the *Harvard Business Review*. In this highly respected journal, articles in this column often present one case first, followed by the comments from two experts. These comments could either support or oppose each other. My teacher asked us to study the case, read through the comments and then form our own point of views on the case. He encouraged us to interpret the case from different perspectives independently in what form that I found pretty practical.

The course brought a possible answer to me. When the open access to clinical research data becomes mainstream, the entire publishing industry, especially the publication of "scholarly journals", would eventually experience revolutionary change. It may no longer focus on the rigid and cold outcomes but it would definitely cares more about the reflection on the problems, update of insights, and integration of science and arts.

AME Medical Review Series is a production of the above thinking. As an attempt, we decided to invite experts internationally to provide their views on a specific topic to share their insights with more clinicians and thus benefit more patients. The first chosen topic for the series is the currently controversial one: conventional surgery versus stereotactic body radiotherapy for

the early stage lung cancer. As the first book to the series, we hope it would give you a glance at the coming changes.

The book series will be written by a group of individual experts who are willing to contribute medical reviews and comments to individuals who are interested in clinical research and medical reviews specifically. The book in your hand may possibly be on a heavy subject but we do hope it is presented in an easier way. It will be more than great if it brings you some thoughts and inspire you in some way.

Stephen D. Wang
Founder and CEO,
AME Publishing Company

One of the reasons that I love the *Lancet* is because it often "intentionally" stirs up some great conversations by publishing articles that can easily cause harsh debates. In this sense, the Journal is somehow another *Vanity Fair*, in which successful men and women come and go; in particular, some new superstars are eager to defeat old masters to declare the coming of a new era. Be defeated? No problem. According to the game rules, the newcomers can again declare that it is not a shame to lose to a senior and, more importantly, they still have more days ahead of them. In addition, you can even invite someone else to fight together. Sometimes the defenders were outnumbered. A good example was that STARS and ROSEL marched along shoulder to shoulder and finally defeated the king of treatment - surgery, as we have witnessed in *Lancet* last year.

As a thoracic surgeon, I am not best qualified to speak on radiotherapy. Two of my friends, Dr. Thomas A D'Amico from Duke Cancer Institute and Dr. Bryan Meyers from Barnes-Jewish Hospital, have talked about this topic with me. Rigorously speaking, the conditions of the conversations differed: once drinking and another not. However, the same conclusion was declared: a good surgery is always better than radiotherapy. I love this conclusion. First, for a thoracic surgeon, "a good surgery" is what we want to pursue. According to Sun Tze in his *The Art of War*, "As what the ancients called a clever fighter is one who not only wins, but excels in winning with ease." Even if lobectomy wins limited resection for a hundred times, will there be no Ginsberg any more? Second, "a poor surgery" is what we are actually worrying about. Poor surgeries can be resulted from various factors including unjustified indications and outdated technology. If conditions still do not allow the introduction of a new treatment, we'd better wait and see or cooperate with other professionals before initiating a debate. Third, there is an old saying that "simplicity is the ultimate sophistication", which makes words superfluous.

As always, we cannot rely too much on a single article. More clinical trials should be performed to further validate the roles of surgery and radiotherapy for early lung cancer. Meanwhile, who wins the debate is not so important; rather, the insights and knowledge shared by all participants during the debate and discussions are more valuable. The "secondary processing" of academic products often plays a key role in increasing the influence and level of academic research. Compared with the *Vanity Fair*, we would rather have a crowd funding version of "Medical Review", in which more authors can present their wisdom, view, and expectations, thus triggering the echo and surging of academic insights and thoughts.

"Memory echoes", emphasized in a Wong Kar-wai's film. Luckily, our wish soon becomes a reality: responding to our call, over 70 professionals have submitted to us their articles, which formed the first volume of the newly unveiled AME Medical Review. I am very happy to present this new series to our readers because it is a new academic product after brainstorming by a group of young authors who believe that argument and debate are the sources of academic productivity. In my mind, it is another valuable attempt by the AME in the secondary processing of literature on hot research topics. This book is composed of a large number of review articles, which are full of arguments and, somehow surprisingly, jokes and endless anecdotes.

I hope you will join me in welcoming this book.

Yaxing Shen

Division of Thoracic Surgery,
Zhongshan Hospital of Fudan University,
Shanghai, China
Barns Jewish Hospital,
Washington University School of Medicine,
St Louis, Missouri, USA

The Path to Lung Cancer Control: Combine Surgery with Stereotactic Radiotherapy

An article on the role of stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiation therapy (SBRT), in the treatment of resectable stage I non-small cell lung cancer (NSCLC) published in the *Lancet* in 2015 has stirred up new debates (DOI: http://dx.doi.org/10.1016/S1470-2045(15)70168-3). This article compared the efficacies of SABR and lobectomy for resectable stage I NSCLC based on the findings of two randomized controlled trials (RCTs) (i.e. the STARS study, initiated by the MD. Anderson Cancer Center; and the ROSEL study, from the Netherlands). Totally 58 patients were enrolled in these two studies. The 3-year overall survival (OS) rates were 79% and 95%, respectively, in the lobectomy group and SABR group, and the 3-year recurrence-free survival (DFS) rates were 80% and 86%, respectively. The SABR group had significantly lower incidences of serious toxic reactions than the lobectomy group. The study concluded that SABR could be well tolerated in resectable stage I NSCLC patients and thus could be an important option for these patients. However, this study has been widely criticized on the grounds that: (I) the sample size was too small; (II) no pathological results were obtained from some patients; (III) the pathology and lymph node staging were not definite in some patients; (IV) the case-fatality rate was unproportionally high in the lobectomy group; and (V) the follow-up duration was too short. In fact, these limitations had been frankly described in the article.

While there are many controversies, one of its conclusions is particularly valuable: SABR is safe and effective in treating resectable stage I NSCLC. Obviously, this was not a perfect study—perhaps there is no perfect research in clinical settings. Despite the presence of these limitations, generations of clinical researchers have constantly launched and updated clinical trials in their search for truth. In my opinion, this study not only presented a new treatment option other than surgery for selected patients with phase I lung cancer but also, and maybe more importantly, provided a key ethical basis for similar clinical research in future—both patients and researchers will be mentally more willing to accept this new technique. It can be expected that more similar multi-center RCTs with larger sample sizes with be available in the coming years and more widely accepted and recognized evidence-based conclusions will be reached. Naturally, we often do not know what we do not know and the truths are often behind paradoxes; a relatively firm conclusion can not be drawn without repeated investigations and discussions. Currently, clinicians from the United States, the United Kingdom, and China are carrying out larger phase III RCTs to compare the efficacies of SABR and surgery. The results might be promising.

As a radiation oncologist, I am particularly interested in these two studies—STARS and ROSEL. From the very beginning (e.g., patient recruitment) of these two studies to their termination and to the publication of research findings in the *Lancet*, I tried to examine this issue from a perspective of evidence-based medicine and avoid any preconception from my education training background that might exaggerates or underestimates the efficacy of this new technique. As we can image, these two studies were particularly challenging. For instance, it was impossible to recruit patients without supports from thoracic surgeons. Even so, patient recruitment remained difficult and slow in both two studies. Eventually only 58 patients were enrolled and the reasons could be complicated. Thus, the thoracic surgeons involved in these studies were great. They examined the lung cancer from the perspective of global cancer control rather than other considerations. In contrast, the views and opinions expressed by a small number of Chinese surgeons were quite disappointing and stunning. After the article was published in the Lancet, some doctors who were involved in lung cancer treatment found that they were affronted. Some thoracic surgeons even wrote articles without any solid evidence to criticize SABR, showing an unbelievable determination to kill this new technique in the cradle. However, the technological progression is an unstoppable and irreversible process. Today, video-assisted thoracoscopic surgery (VATS) has become one of the most important treatments for lung cancer, which was unimaginable three decades ago. However, any controversy or objection must be based on scientific evidences, not "take for granted". I always support any evidence-based objection—it was these reasonable and justifiable objections that promoted the development of human technology.

Cancer is our common enemy. Cancer control requires the joint efforts of medical staff in surgery department, oncology department, radiotherapy department, pathology department, nursing department, and many other clinical and supporting departments. Lung cancer control remains challenging in China due to delayed and inadequate tobacco control and

environment (in particular air) pollution. According to the statistical data released by the National Cancer Center in 2015, lung cancer ranked the first in China in terms of both prevalence and mortality rate. Such a heavy disease burden reminds us all the time that lung cancer control requires the joint efforts of multiple disciplines, and different treatments from different disciplines are supporting rather than competing with each other. In contrast, the two studies published in the *Lancet* confirmed the effectiveness of SABR but did not deny the leading role of surgery in treating the early lung cancer. SABR should be a good supplement to surgical treatment. Thus, the lung cancer patients have a new choice and the doctors have a new weapon. Dr. Joe Y. Chang from the MD. Anderson Cancer Center was among the authors of this *Lancet* article. He wrote on social media, "*My suggestions are: first, we must be open to any criticism and try our best to carry out the ongoing RCTs; second, with a goal of achieving excellence, we must constantly improve the capability and quality of radiotherapy technology, so as to ensure the treatment effectiveness; and third, we must embrace the future by achieving the reasonable combination of chemotherapy, targeted therapy, radiotherapy, and immunotherapy. We shall remove professional boundaries and embrace new ideas, no matter whether such ideas come from chemotherapy, surgery, or radiotherapy. We must work together to fight against cancer, which is also a global dilemma*."

I fully agree with Dr. Chang. While we must do a good job in our own field, we should also actively seek cooperation with other professionals, and such cooperation should not be confined to the areas of clinical medicine. As seen in the history of medicine, scientific&technological innovations and interdisciplinary cooperation have played decisive roles in the development of medicine. "Science and technology are the first productive force." This is not a political slogan; rather, it is a universal truth that also applies medical science & technology. Without science and technology development during the Renaissance, medicine might remain in the era of traditional empirical medicine that was taught by word of mouth; without the advances in modern disciplines including physics, chemistry, biology, and materials science, the modern medicine might still wander between science and non-science. As we currently are in an era that the science & technology develops rapidly, we might be far left behind and even mislead our patients if we were too conservative to adopt new technology.

In view of the hot discussions on SABR and its potential therapeutic values, many journals under the AME Publishing House had invited 73 top thoracic surgeons and radiologists from 11 countries to share their insights on the subject of "Efficacy of SABR *vs*. Lobectomy in Treating Resectable Stage I Non-small cell Lung Cancer (NSCLC)". This book is a collection of all these articles that may be particularly interested by our readers. The articles make detailed summaries of existing scientific evidences and clinical experiences, give objective elaboration on the current arguments, and shed light on future research directions and topics. The rich information in this book will for sure be valuable for all the colleagues who are engaged in lung cancer management. As always, any further comments on this topic will be warmly welcomed. As the publisher, we hope our subtle efforts will contribute to the fight against lung cancer.

Zhirui Zhou
Department of Radiation Oncology,
Tumor Hospital of Jilin Province,
Changchun, China;
Department of Radiation Oncology,
Fudan University Shanghai Cancer Center,
Shanghai, China

Surgery has historically been considered the only hope for a cure of lung cancer since 1933, when Dr. Evarts Graham performed the first successful pneumonectomy for lung cancer. The idea was to resect tumor and adjacent lymph nodes plus a generous surgical margin. Soon thereafter, surgery (lobectomy or pneumonectomy with lymph node dissection or sampling) became the standard treatment for patients with localized disease who were physically able to tolerate the operation. However, surgical resection is associated with significant morbidity and mortality; an analysis of a nationwide inpatient sample database indicated that about 45% patients who undergo surgery develop severe postoperative complications (1). Surgical mortality rates have ranged from 1.8% to 3.8% at 30 days and 4% to 6.5% at 90 days. Even for patients with stage I lung cancer, 5-year overall survival rates after surgery range from 60% to 80%; roughly 5% to 10% patients experience recurrence in the hilar or mediastinal lymph nodes, and another 10% to 20% develop distant metastasis even though the mediastinal lymph nodes had been sampled or dissected (2). Clearly, there is room for improvement.

With the wide use of lung cancer screening programs, more early-stage lung cancers are anticipated to be detected. The median age of patients with lung cancer is 70 years at diagnosis (http://seer.cancer.gov/csr/1975_2012). Many such patients will have comorbid conditions such as chronic obstructive pulmonary disease (COPD), cardiovascular disease, diabetes and others. Thus it remains crucial to develop curative treatment that has minimal side effects. The recently invented technique of video-assisted thoracoscopy lobectomy (VATS) seems to reduce the rate of severe postoperative complications somewhat, from 45% to 41%, but has not changed operative mortality rates relative to open thoracotomy (1). Lymph node sampling or dissection seems to be compromised in some cases, but overall survival rates remain similar for patients treated with either approach.

Technologic innovations allowing the implementation of image-guided stereotactic ablative radiotherapy (SABR, also called stereotactic body radiation therapy, SBRT) have enabled radiation oncologists to deliver tightly focused, high biologically effective doses of radiation (>100 to 130 Gy), enough to kill nearly all cancer cells within the target, to early-stage lung cancers; SABR has produced local control rates in excess of 95%. With the use of modern-day disease staging procedures such as computed tomography (CT), positron emission tomography (PET)/CT, and endobronchial ultrasonography (EBUS), rates of lymph node recurrence and distant failure after SABR for stage I NSCLC are 5%–13% and 15%–20% (3), rates that are similar to those after surgical resection even though elective lymph node irradiation is not given. SABR has become the standard of care for medically inoperable stage I NSCLC (4), and its implementation has improved national lung cancer survival rates (5).

Nevertheless, the question remains: which is better for operable stage I NSCLC, surgery or SABR? Most propensity-matched retrospective studies have shown the two modalities to produce similar overall survival rates (6), and only a few studies have indicated a survival advantage for surgery. However, retrospective comparisons inherently have selection bias, and so the best approach is to conduct randomized studies. Unfortunately, all of the randomized studies that have been attempted to date, that is, the STereotActic Radiotherapy *vs.* Surgery (STARS) trial, the Radiosurgery Or Surgery for Early Lung cancer (ROSEL) trial, and the ACOSOG Z4099/RTOG 1021 trial, "A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)," were closed prematurely because of poor enrollment, chiefly because the treating physicians tended to favor surgery. Pooled analysis of the STARS and ROSEL trials showed that SABR produced better overall survival and similar progression-free survival (7). The authors of that analysis concluded that "SABR has emerged as a noninvasive standard treatment alternative to surgery for elderly patients and for patients with clinically significant comorbidities and should be considered as an option for treatment of operable stage I NSCLC." These studies, and this analysis, have trigged significant debate in the thoracic oncology community. The significance and limitations have been widely discussed, and newer randomized studies have been opened for enrollment in the United States [Veterans Affairs Lung cancer surgery Or stereotactic Radiotherapy (VALOR)]; Sublobar Resection (SR) versus Stereotactic Ablative Radiotherapy (SAbR) in High Risk Patients with Stage I NSCLC (STABLE-MATES), Europe [Stereotactic Ablative Radiotherapy *vs.* surgery in patients with peripheral stage I non-samll cell lung cancer considered higher risk of complications from surgical resection (SABRTOOTH)], and China [Radical Resection *vs.* Ablative Stereotactic Radiotherapy in Patients With Operable Stage I NSCLC (POSTILV)].

Interestingly, preliminary findings support the supposition that SABR can not only kill cancer cells but also release tumor-associated antigens, which can function as a cancer-specific "vaccine" in situ that can fight local, regional, and distant recurrence. Combinations of SABR with immunotherapies such as checkpoint inhibitors ("iSABR") could significantly

improve treatment efficacy and cure rates (8). Undoubtedly these and other combinations of technologic and biologic advances will lead to fundamental changes in the way we treat lung cancer.

This book provides a comprehensive review of SABR and its use for medically inoperable or operable early-stage lung cancer or for oligometastases lung cancer. Until now, the question of which treatment is optimal for medically operable stage I lung cancer—surgery or SABR?—remains controversial. Certainly additional randomized studies are needed. This topic should not represent a battleground between thoracic surgeons and radiation oncologists. Rather, attention should be directed toward the battle our patients are fighting. Lung cancer is still the number 1 cancer killer in the world. No one, neither patients nor physicians (including surgeons and radiation oncologists), is satisfied with the status quo for lung cancer outcomes. Discoveries in the evolution of technology and biology are providing unique opportunities to expand our understanding of lung cancer and how to eliminate it. As Dr. Graham once said, "*Perhaps in the future some non-surgical method will be discovered which will be not only more simple in its execution but more reliable in its results than a surgery.*" It is quite possible that certain patients will benefit more from surgery, and others will benefit more from SABR. It is our job as physicians to identify which patients belong to which group, so that we can provide truly individualized care.

References

1. Paul S, Sedrakyan A, Chiu YL, et al. Outcomes after lobectomy using thoracoscopy vs thoracotomy: a comparative effectiveness analysis utilizing the Nationwide Inpatient Sample database. Eur J Cardiothorac Surg 2012;43:813-7.
2. Lou F, Huang J, Sima CS, et al. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg 2013;145:75-81.
3. Senthi S, Lagerwaard FJ, Haasbeek CJ, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol 2012;13:802-9.
4. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
5. Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. J Clin Oncol 2010;28:5153-9.
6. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. JAMA Surg 2014;149:1244-53.
7. 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.
8. Bernstein MB, Krishnan S, Hodge JW, et al. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? Nat Rev Clin Oncol 2016. [Epub ahead of print].

Joe Y. Chang, Professor, Director
Stereotactic Ablative Radiotherapy,
MD Anderson Cancer Center

The Patient Best Interest

For the past decade, stereotactic ablative radiotherapy (SABR) has represented one of the major innovations in lung cancer management. Along with targeted chemotherapy, minimally invasive (VATS and robotic) surgery, and, more recently, immunotherapy, SABR has paved the way for a new interpretation of the role that each clinical specialty possesses in the multidisciplinary approach to lung cancer. Excellent local control with reduced morbidity have been clamed as significant advantages of SABR which, as a viable alternative to surgery, has been established as the treatment of choice for inoperable patients with early lung cancer. However, some hurdles still remain before considering SABR also in the management of primarily operable patients. These include absence of reliable data of long-term survivals obtained from randomized trials, the incidence of nodal failures, the unclear ability to treat centrally located tumors without generating important toxicity, and, the issue of late post-treatment morbidity. This book is meant to shed some light on the concept emerging from the literature that SABR may yield the same locoregional control compared to sublobar resections in operable patients and that the choice of the favored therapeutic modality rests on the multidisciplinary group based on the individual patient's characteristics. In addition, the role and the current invasiveness of surgery is discussed especially in light of the abnormal report of surgical outcomes presented in part of the SABR literature with special attention to the controversial concept of medical inoperability. In conclusion, it is obvious that the answers we are expecting to address the above mentioned issues need to come from adequately powered randomized trials comparing SABR to surgery, where clear surgical and SABR criteria for patient recruitment are to be defined to serve – as always – only the patient best interest.

Gaetano Rocco, MD, FRCSEd, FEBTS, FCCP
Director, Department of Thoracic Surgical and Medical Oncology,
Chief, Division of Thoracic Surgery,
Istituto Nazionale Tumori,
Fondazione Pascale,
IRCCS, Naples, Italy

The Competition

"You can't look at the competition and say you're going to do it better. You have to look at the competition and say you're going to do it differently."

—Steve Jobs

In the battle against lung cancer, there has traditionally been a clear division of labor. Advanced disease is deemed 'inoperable', and hence has long been the exclusive domain of oncologists. Early stage disease, on the other hand, is well recognized to be best treated by surgical resection. Thoracic surgeons and oncologists have co-existed and co-operated relatively harmoniously in this symbiosis.

However, in recent years, something has emerged that threatens to disrupt this relationship. Some would call it a Disruptive Technology, such is its revolutionary impact on lung cancer management. One is speaking of course about Stereotactic Body Radiation Therapy (SBRT).

What SBRT promises is fantastically effective local therapy, but without the potential trauma—and patient anxiety—often associated with major thoracic surgery. Results in recent years have amply demonstrated its utility and efficacy. Indeed, SBRT has gradually emerged as not only an 'option' for patients that cannot tolerate surgery, but a possible outright alternative to surgery. No other advance in oncological therapy has had such impact. Ablative therapy and even targeted therapy have never achieved what SBRT looks to achieve: to potentially replace surgery for the treatment of early stage lung cancer.

For the first time in decades, lung cancer surgeons feel that their raison d'être is under threat. The delicate symbiosis is being upset by the oncologists moving in on their 'turf'. Epitomising the many studies showing the merit of SBRT, the 2015 *Lancet Oncology* paper by Chang *et al*. demonstrating the possible 'superiority' of SBRT over surgery for early stage lung cancer sent shockwaves through the lung cancer community (1). Surgeons have already indicated that they will not go down without a fight, pointing out the flaws which may fundamentally undermine many such SBRT studies (2).

But is this really a 'zero-sum' game? Is any gain by clinicians practising SBRT necessarily a loss by thoracic surgeons, and vice-versa? A visionary like Steve Jobs would probably say no. Apple did not grow into the 21st Century by building a 'better' Apple II or Macintosh desktop computer. It succeeded by going in a completely different direction: inventing the iPhone and iPad.

For thoracic surgeons, the struggle should not be just about proving surgery is 'better' than SBRT. An innovation as powerful as SBRT can never be wished away. Instead, surgeons need to learn to evolve in the new era where SBRT exists, and learn to form a new symbiosis. How can surgery complement SBRT (or targeted therapy for that matter)? How should the multi-disciplinary team function with the increasing pace of new innovations breaking onto the lung cancer scene?

For SBRT practitioners, the fight should also not be with surgeons over the 'traditional' patient with early stage lung cancer. Instead, the vision should be to reach patients who would previously have had no other options. It is far more important, for example, to explore new territories in terms of treatable patients than to just scrap over old ones. Treating more different patients is perhaps a nobler endeavour than just treating the same ones a little better.

As surgeons and oncologists—hopefully—find a new equilibrium in the SBRT era, the ones who stand to benefit will undoubtedly be the patients. Good clinicians striving to treat cancer not only 'better', but differently will surely lead to greater hope.

This book contains the word 'versus' in its title. This is deliberately provocative, to be sure. However, healthy competition may bring rewards for patients. The articles in this book are written by recognized experts in the field of lung cancer therapy. Perspectives from both the SBRT and surgical camps are well represented, and the arguments on either side are balanced and maturely reasoned. Studying the evidence and the opinions from each angle as portrayed in this book is undoubtedly a fine way to steer the competition in a healthy direction.

For the sake of patients, let us all look at the competition clearly and consider how we can do things differently!

References

1. 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;16:630–37.
2. Cao C, D'Amico T, Demmy T, et al. International VATS Interest Group. Surgery versus SABR for resectable non-small-cell lung cancer. Lancet Oncol 2015;16:e370-1.

Alan D. L. Sihoe
Clinical Associate Professor, Department of Surgery, The University of Hong Kong, China
Chief of Thoracic Surgery, The University of Hong Kong Shenzhen Hospital, China
Guest Professor, Department of Thoracic Surgery, Tongji University Shanghai Pulmonary Hospital, China

Anatomic major pulmonary resection has long been considered the standard of care for Stage I with cure rates of 50–90% (1). Traditionally, the standard treatment was too agressive: open approach by means of thoracotomy, anesthetic control with a double lumen tube, epidural ,central venous catheter, arterial line and urinary catheter.

Stereotactic body radiation therapy (SBRT) has evolved over the past 20 years and revolutionized the management of early stage NSCLC. Compared to conventional radiation therapy, SBRT offers superior outcomes, lower costs and greater patient convenience (2). The role of minimal invasive surgery and stereotactic body radiation therapy in stage I NSCLC are evolving, particularly for marginally operable patients and the elderly population. SBRT is generating promising results in inoperable patients, with local control rates of 90% or higher in Stage I of the disease.

The management of Stage I NSCLC has now developed into a focus of intense debate between surgeons and radiation oncologists. Thoracic surgeons argue that SBRT does not provide adequate pathological staging and that it is a local treatment only, without the removal of the tumor. This is in contrast to many radiation oncologists who argue that surgery has a higher morbidity while SBRT offers local control and cancer outcomes approaching surgical resection, but with a lower risk of treatment-related morbidity, thus making SBRT the treatment of choice for medically inoperable and many high-risk surgical candidates.

However, in the most critical issue of cancer therapy, the literature comparing VATS and SBRT has suggested that survival data may not be entirely in favor of SBRT (3). For example, one recent study suggested that stereotactic body radiotherapy (SBRT) offers lower immediate mortality and toxicity. Over the longer term, however, there was more benefit with surgery over SBRT (4). These findings highlight the importance of looking at the long-term benefit to patient life expectancy rather than to the short-term benefits of a treatment when reviewing and interpreting future comparisons of SBRT and surgery. In another recent propensity matched study of 117,618 patients, it was demonstrated that there was improved survival with surgery compared with SBRT. However, rigorous prospective studies are needed to optimize the patient selection criteria for SBRT in the high-risk surgical population (5). It was further reported that VATS lobectomy offers better results than SBRT in the treatment of patients with pathologically confirmed early stage NSCLC (6).

Perhaps the road ahead may be determined by defining an appropriate role for SBRT vis-a-vis surgery. Today, with the very rapid advances in medical oncology through the development of new chemotherapy with less toxicity and major effectiveness, as well as SBRT, the role of a thoracic surgeon is to offer the patient the best oncologic procedure with the least surgical invasiveness and anaesthetic such as uniportal VATS and non intubated techniques. The combination of radiology and thoracic surgery techniques within the hybrid operating theater may open doors to new surgical and ablative radiation techniques that can be potentially safer, more effective and more economical for our patients. The comparative mortalities and toxicities of these treatments for patients of different life expectancies are unknown. We are expecting in the future that well designed and large randomized trials will be conducted comparing sublobar resection and SBRT for local control, quality of life and overall survival.

In the meantime, thoracic surgeons are continually aiming to find the way to offer our patients the least invasive approach possible for removing the lung cancer. Improvements in anaesthetic techniques such as non-intubated uniportal VATS, may further quicken postoperative recovery allowing the tumor resection to be performed in an ambulatory setting. Over the past 2 decades VATS has further evolved into a sophisticated technique capable of performing the most complex thoracic procedures. Additionally, a rapid progress in instrument design and technology have brought developments of narrower and more angulated endostaplers, sealing devices for vessels, and adapted and refined thoracoscopic instruments (7). Furthermore the surgery is evolving more and more to segmental and sublobar resections for early stages of NSCLC, preserving lung parenchyma and offering similar oncological results when compared with lobectomy. Evidence from current literature, suggests that VATS segmentectomy could be equivalent to VATS lobectomy in terms of overall and disease-free survival, postoperative complications and mortality (8). The development of future technology such as wireless remote camera systems, subxiphoid approach, embryonic natural orifice transluminal endoscopic surgery (e-NOTES) or nanorobotic surgical techniques will help to reduce surgical access trauma and allow a faster recovery to our patients.

This book offers a balanced overview of the latest advances in both surgical and SBRT developments. This should hopefully provide the reader with a comprehensive understanding of the current debate, helping guide even better management of our lung cancer patients in the future.

References

1. Vansteenkiste J, De Ruysscher D, Eberhardt WE, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi89-98.
2. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352-8.
3. Verstegen N, Oosterhuis J, Palma D, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 2013;24:1543-8.
4. Yu JB, Soulos PR, Cramer LD, et al. Comparative effectiveness of surgery and radiosurgery for stage I non-small cell lung cancer. Cancer 2015;121:2341-9.
5. Puri V, Crabtree TD, Bell JM, et al. Treatment Outcomes in Stage I Lung Cancer: A Comparison of Surgery and Stereotactic Body Radiation Therapy. J Thorac Oncol 2015;10:1776-84.
6. Hamaji M, Chen F, Matsuo Y, et al. Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer. Ann Thorac Surg 2015;99:1122-9.
7. Ng CSH. Uniportal video assisted thoracic surgery: a look into the future. Eur J Cardiothorac Surg 2015;49:i1–2.
8. Kodama K, Higashiyama M, Okami J, et al. Oncologic outcomes of segmentectomy versus lobectomy for clinical T1a N0 M0 non-small cell lung cancer. Ann Thorac Surg 2016;101:504-11.

Diego Gonzalez-Rivas, MD, FECTS

Director Uniportal VATS Training Program,
Shanghai Pulmonary Hospital,
Department of Thoracic Surgery and Lung Transplantation
Coruña University Hospital and
Minimally Invasive Thoracic Surgery Unit (UCTMI),
Coruña, Spain

This collection of papers from Europe, North America and Asia highlight current developments and viewpoints in the field of stereotactic ablative radiotherapy (SABR) for early-stage lung cancer. SABR was first described by Swedish investigators in 1995 (1). This issue provides a contemporary global perspective of leading thoracic oncologists, and highlightd both consistently high local control rates observed following guideline-specified SABR, and a low incidence of high-grade toxicity. Mechanistic aspects of local effect though vascular damage and/or immune mechanisms, are reviewed. The controversies surrounding the use of SABR for centrally-located tumors are debated, with the obvious conclusion being that reliable dose constraints need to be identified.

A surgical viewpoint notes that the growing use of SABR for patients who are fit to undergo surgery, remains controversial. However, well-argued, critical commentaries from radiation oncologists indicates that they have not been disheartened by the failure of the first generation of trials comparing surgery and SABR to complete accrual. Much of the emerging evidence for use of SABR in fitter patients comes from comparative effectiveness research (CER) (2). CER has been defined as the "generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition" (3). CER complements findings derived from randomized clinical trials, and can address important questions that cannot, and will not be ever addressed in the context of a clinical trial (4). Although selection and referral biases that can confound traditional forms of observational research, this may be less of a problem with population-based observational studies, that include all patients within a given jurisdiction.

While a new generation of randomized clinical trials comparing SABR and surgery are in progress (5), developments in early-stage NSCLC will continue to be influenced by CER. The 'value' of cancer care provided has now assumed a high societal priority in both the European Union and the United States (6,7). Furthermore, there is growing awareness of the potential for financial toxicity in lung cancer treatments (8). Both CER and clinical trials are expected to provide important insights in the near future with regards to 'value' in the treatment of early-stage NSCLC in patients fit to undergo surgery.

References

1. Blomgren H, Lax I, Näslund I, et al. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 1995;34:861-70.
2. Louie AV, Palma DA, Dahele M, et al. Management of early-stage non-small cell lung cancer using stereotactic ablative radiotherapy: Controversies, insights, and changing horizons. Radiotherapy and Oncology 2015;114:138-47.
3. Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. Ann Intern Med 2009;151:203-5.
4. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. Br J Cancer 2014;110:551-5.
5. Siva S, Ball D. Curing operable stage I non-small cell lung cancer with stereotactic ablative body radiotherapy: the force awakens. Oncologist 2016. [Epub ahead of print].
6. Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 2015;26:1547-73.
7. Schnipper LE, Davidson NE, Wollins DS, et al. American Society of Clinical Oncology Statement: a conceptual framework to assess the value of cancer treatment options. J Clin Oncol 2015;33:2563-77.
8. Lathan CS, Cronin A, Tucker-Seeley R, et al. Association of financial strain with symptom burden and quality of life for patients with lung or colorectal cancer. J Clin Oncol 2016. [Epub ahead of print]

Professor Suresh Senan
Department of Radiation Oncology,
VU University Medical Center
De Boelelaan 1117, Postbox 7057
1007 MB Amsterdam, The Netherlands

Stereotactic body radiation therapy or stereotactic ablative radiation therapy (SABR) has revolutionized the way early-stage lung cancer can be treated with radiotherapy. Replacing the conventional 6-7 week treatment course, SABR is delivered over 2-3 weeks, providing a more convenient, resource-efficient treatment, which has improved local control rates and overall survival. The primary role for SABR has been as an alternative to surgery when surgery is declined by the patient or poses too high a risk. The latter pertains to an ever increasing proportion of lung cancer patients, as the elderly are more frequently plagued by other smoking related co-morbidities and poor pulmonary function. In this setting SABR has proven to be an effective and well-tolerated treatment, providing a potentially curative option for those who may have had none previously. Evidence of this is demonstrated by its rapid adoption in clinical practice worldwide and is now recommended by many major bodies as first line treatment in medically inoperable patients.

The development of technology has been the foundation in allowing the safe administration of SABR doses, which rely on precise tumour localization and treatment delivery. Increased access to technologies, such as 4-dimensional computed tomography and cone-beam computed tomography, has allowed widespread use of SABR outside expert academic institutions. Introduction of SABR into a clinical department should be carried out with great vigilance, necessitating appropriate training and expertise, accompanied by a robust quality assurance program.

This book stands as a collection of work from experts in radiation oncology and thoracic surgery, providing an in-depth, thought-provoking overview of this long-standing and important debate on surgery versus SABR for early-stage lung cancer. Its chapters will explore the history, current evidence, clinical experience, controversies and future directions of this complex issue. This book aims to help guide clinicians on the opposing treatment options and their associated benefits, to provide evidence-based, patient-centred solutions for their patients.

The proven success of SABR for medically inoperable patients has lead to the questioning of its feasibility in operable patients. Studies have reported SABR outcomes equivalent (and sometimes superior) to surgery, suggesting equipoise between the two treatment options, however a lack of level one evidence prevents this from being clinically accepted. The opening of two randomised control trials provided hope that an answer would be found, but disappointing accrual has lead to the premature closing of both. Outcomes of the limited patients that were accrued have now been published and have sparked much debate. Whilst definitive SABR is appearing to be a viable first-line option for operable patients, many of the results in these and other studies on the issue, have been flawed by biases, all of which will be discussed in depth within this book.

Further controversy surrounds the utilisation of SABR for centrally located tumours, the treatment of patients without histological diagnosis, the issue of potential lymph node metastasis and the influence of surgical technique and perioperative care on surgical outcomes. Whilst SABR has been adopted rapidly, caution needs to be taken when interpreting the evidence. Inconsistencies in post-SABR follow-up of patients exist and arise from the difficulty in distinguishing between radiation-induced changes and tumour recurrence. The complex interpretation of post-treatment imaging and its impact on deciding next line of treatment, stresses the need for a multidisciplinary approach, particularly when we are seeing younger, fitter patients receiving SABR.

In an age where populations are ageing and the use of lung cancer screening tools are on the rise, the number of patients who are candidates for SABR will grow. The need for high quality randomized data has never been greater. Every effort should be made to enrol patients on prospective randomized trials. In the meantime, the treatment options need to be discussed in a multidisciplinary approach and thoroughly presented to patients. The choice of treatment needs to remain patient-centred and account for individual patient preferences.

Katrina Woodford
Alfred Health Radiation Oncology,
The Alfred, Melbourne, Victoria, Australia

Lung cancer is the most common cause of death by malignancy in the world, and it is responsible for as many deaths as colon, breast, pancreas and prostate cancers combined in the US. With the introduction of screening for lung cancer, the development of more precise radiographic techniques, and an aging population worldwide, increasing numbers of patients will be identified with small, early stage lung cancer, many of whom are elderly. In this setting, some patients will be treated with stereotactic body radiotherapy (SBRT) and some will be treated surgically. Which is better? How will we decide which therapy to use?

This volume, *Surgery versus Stereotactic Body Radiation Therapy for Early-Stage Lung Cancer*, presents to most up to date data available regarding the relative nature, purpose, risks and benefits of the 2 techniques. The current evidence, relevant controversies, and future directions are critically discussed by an international panel of experts, from Asia, Europe, and North America. The editors have compiled more than 25 outstanding contributions that present a fair and balanced treatment of this critically important subject.

In years to come, it is hoped that prospective, randomized trials will clearly establish which of the 2 therapies would be best in any given patient. Until then, a complete knowledge of the current data, a deep understanding of the relevant studies, and clear perception of future trends is essential to optimize the management of an increasing population of patients with early stage lung cancer.

Thomas A. D'Amico, MD

Gary Hock Endowed Professor of Surgery,
Chief, Section of General Thoracic Surgery ,
Duke University Medical Center, DUMC Box 3496,
Duke South, White Zone, Room 3589,
Durham, North Carolina 27710, USA

In this compilation, Editors Dr. Yaxing Shen and Dr. Zhirui Zhou have invited well known international experts in the field of lung radiotherapy to have their recently published articles on the topics relevant to lung stereotactic body radiotherapy (SBRT) included in this compendium. Of note, only two of the 30 articles appear to be authored by thoracic surgeons. These articles were previously published in a variety of journals, some peer reviewed, some not, written with different purposes and to a range of audience. Some are brief summaries, some are editorials, others are more detailed discussions of issues, some are extensive reviews of evidence, with 100 or more references, some are presentation of original data, and some focus on practical and very clinically relevant issues. These articles come from authors from many different institutions in North America, Europe, Australia and Asia. Importantly to note, articles were published in different years, from 2011 to 2015. This is important to bear in mind while reading, as the current evidence is constantly changing; this is particularly relevant for critical appraisal of review articles. Thus, reader should be paying attention to the year that the article was originally written and to which data is included in the review, as a more recent publication might possibly lead to a different conclusion.

By design of such a compilation of "best of that we have access to", there is repetition, ie several articles address the same issue, sometimes with same conclusions and arguments and sometimes with different ones. A reader with time on hand may find a "contrast and compare" analysis of articles addressing same topics quite informative. The titles of the sections are not as informative as they could be: there is considerable overlap between the topics covered in the first section "Current Evidence" and the next section entitled "Clinical Experience, Controversy and Debate". That being said, a compilation of these articles all in one place allows a reader to focus on what the many world recognized leaders in their field have to say on the evidence behind SBRT, especially with respect to comparison to surgery, and on the topic of SBRT for operable patients. There are several articles on how to plan and deliver SBRT, with specific focus on quality assurance and safety. A number of articles focus on SBRT for central tumors, including a transcontinental debate on the issue (*Woodford and Senthi vs Nestle and Belderbos*); debates of this type have become very popular at meetings and their inclusion in a publication makes for a good read.

In summary, this book offers a plethora of reading for someone who wants to become familiar with principles, practice and evidence behind lung SBRT. And for those who are already quite familiar with lung SBRT and follow the literature, there are still chapters that are well worth reading. For those readers, I would particularly highlight the article by Rusthoven *et al*. addressing the implications of low-accruing randomized trials of surgery and SBRT and an interesting article on radiobiology by Karam and Bhatia.

Dr. Andrea Bezjak, MDCM, MSc, FRCPC
Professor, Department of Radiation Oncology, University of Toronto,
Leader, Lung Cancer Site Group,
Princess Margaret Cancer Center,
University Health Network, Toronto, Ont, Canada

SABR for early-stage operable lung cancer—is it the coming Wolf?

The wolf has a winning game when the shepherds quarrel, as the old saying goes. No thoracic surgeons or radiation oncologists have failed to be shocked by the provocative pooled analysis of two randomized trials comparing lobectomy and stereotactic ablative radiotherapy (SABR) for medically operable patients with T1-2a (<4 cm) N0 M0 non-small cell lung cancer (NSCLC) (1). It is reasonable for radiation oncologists to congratulate each other that the foundation of surgery as the gold-standard for operable NSCLC has been shaken, for the first time, by contradictory data (2). While many of us thoracic surgeons chaffed at the use of truncated trials and incredibly high surgical morbidity and mortality in the study, deep in our heart we must be crying out in alarm of the coming wolf. But where is the wolf coming from?

Surgery has remained the standard approach for early stage lung cancers for more than half a century. The recommended procedure for non-small cell lung cancers had been *anatomical lobectomy* with systemic *lymph node dissection* via *open thoracotomy* in the past decades. But things have changed significantly recently. First we witnessed the transition from open approach to minimally invasive procedures including video-assisted thoracoscopic surgery (VATS), which has greatly diminished the risks and trauma associated with lung cancer surgery (3). The initial criticism of such innovative techniques are still vivid in our memory when VATS has now become the preferred approach in our daily practice. One important lesson learned from the evolution of minimally invasive surgery is that all novelties should not be readily denied or embraced. Fortunately most surgeons have had a conscious mind in pursuing the right course of evolution.

In the meantime, the other two elementary components of lung cancer surgery have not been spared either. The ACOSOG Z0030 study demonstrated that for clinically stage Ia lung cancers, systemic lymph node dissection would offer no additional benefit either in the effect of staging or long-term outcomes comparing with lymph node sampling alone (4), although it adds little morbidity to a pulmonary resection either (5). One important issue sometimes neglected is that in the ACOSOG Z0030 study, patients were randomized only if no lymphatic involvement was revealed after systemic nodal sampling. The authors have also made it clear that the results of the study should not be extrapolated indiscreetly to patients with higher T stage or known N2 diseases. Neither should the study be used against rigorous mediastinal staging during evaluation of early stage lung cancers (4).

Then there have also been increasing query on the extent of resection recently. The best available evidence favoring lobectomy over limited resections for T1N0M0 lung cancers came from the Lung Cancer Study Group trial published in 1995 (6), which demonstrated that comparing to standard lobectomy, sublobar resections were associated with 75% increase in recurrence, tripling of local recurrence, 30% increase in overall death, and 50% increase in cancer death. However, with increasing small lung cancers detected at an earlier stage (7), sublobar resections, especially segmentectomy have revived as acceptable options in selected patients (8). Accompanying the increased use of CT screening for early lung cancer is the understanding of a special group of air-containing lesions histologically presented as adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA), which seldom metastases and has a near 100% disease-specific survival after resection (9). For lower grade malignancies like AIS and MIA, even a wedge resection with enough margin may be enough. Yet, even the results from the two ongoing phase III trials (10,11) may not be able to give out a definite answer to this issue because of the intrinsic pitfalls in their study design (12).

So what are the contemporary principles for lung cancer surgery? It should never be merely the physical removal of the tumor per se. It also means histological diagnosis and accurate staging of the disease, in addition to satisfactory local control and long-term survival, at an acceptable risk and functional loss. With increasing reports on SABR for small lung cancers, it is now referred as 'radiational surgery'. But if sublobar resections could not yet be fully accepted because of the Lung Cancer Study Group trial results, how could another '*local*, *physical*' therapy with a margin of only a few millimeters and without precise staging or even histological diagnosis do better? Among all the argument around SABR and surgery, attention has seldom been paid to the reasons for the ROSEL (13) and the STARS (14) studies to be closed prematurely. In fact the poor accrual in these two trials clearly suggests that if we physicians fail to recognize the underlying reasons for improved outcome after SABR or limited resections, our patients have obviously voted for us with their feet. More common sense is needed in this debate than scientific deduction.

Someday, patients with lung cancer, as with most other malignancies, may no longer need to endure the pain and the

risk of our scalpel. But instead of meeting the trouble halfway, thoracic surgeons should persist in the effort of reducing the surgical risks and trauma while upholding the oncological principles build upon reliable evidences. The *real wolves* for both surgical and radiation oncologists are always the disease itself and treatment-related morbidities. We are treating different patients with different diseases at a different era. What we need to continue is to do things differently, and do them better.

References

1. 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 randomized trials. Lancet Oncol 2015;16:630-7.
2. Rusthoven CG, Kavanagh BD, Karam SD. Improved survival with stereotactic ablative radiotherapy (SABR) over lobectomy for early stage non-small cell lung cancer (NSCLC): addressing the fallout of disruptive randomized data. Ann Transl Med 2015;3:149.
3. Paul S, Altorki NK, Sheng S, et al. Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: A propensity-matched analysis from the STS database. J Thorac Cardiovasc Surg 2010;139:366-78.
4. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non–small cell carcinoma: Results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg 2011;141:662-70.
5. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. Ann Thorac Surg 2006;81:1013-9.
6. Lung Cancer Study Group, Ginsberg RJ, Rubenstein LV. Randomized trial of lobectomy versus limited resection for T1N0 non-small cell lung cancer. Ann Thorac Surg 1995;60:615-22.
7. Aberle DR, Berg CD, Black WC, et al. The National Lung Screening Trial: overview and study design. Radiology 2011;258:243–53.
8. Cao C, Chandrakumar D, Gupta S, et al. Could less be more?- A systemic review and metaanalysis of sublobar resections for non-small cell lung cancer according to patient selection. Lung Ca 2015;89:121-32.
9. Travis WD, Brambilla E, Noguchi M, et al. IASLC/ATS/ERS international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-85.
10. Nakamura K, Saji H, Nakajima R, et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607L). Jpn J Clin Oncol 2010;40:271-4.
11. CALGB 140503. A phase III Randomized trial of lobectomy versus sublobar resection for small (2 cm) peripheral non-small cell lung cancer. Available online: http://www.cancer.gov/about-cancer/treatment/clinical-trials/search/view?cdrid=555324
12. Taiolo E, Yip R, Olkin I, et al. Survivals after sublobar resection for early stage lung cancer: Methodological obstacles in comparing the efficacy to lobectomy. J Thorac Oncol 2016;11:400-6.
13. ROSEL. Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer (ROSEL). Available online: https://clinicaltrials.gov/ct2/show/NCT00687986
14. STARS. Randomized Study to Compare CyberKnife to Surgical Resection In Stage I Non-small Cell Lung Cancer (STARS). Available online: https://clinicaltrials.gov/ct2/show/record/NCT00840749?term=NCT00840749&rank=1

Wentao Fang, Yangwei Xiang, Chenxi Zhong
Department of Thoracic Surgery,
Shanghai Chest Hospital,
Jiaotong University Medical School,
Shanghai, China

Acknowledgements

Dedicated Cover Painting from

Zhijing Xu

School of Medicine Shanghai Jiaotong University

Surgery versus Stereotactic Body Radiation Therapy for Early-Stage Lung Cancer
(FIRST EDITION)

Contributors

Honorary Editors

Qun Wang
Department of Thoracic Surgery, Shanghai Zhongshan Hospital of Fudan University, Shanghai, China

Joe Y. Chang, Professor, Director
Stereotactic Ablative Radiotherapy, MD Anderson Cancer Center

Gaetano Rocco, MD, FRCSEd, FEBTS, FCCP
Director, Department of Thoracic Surgical and Medical Oncology, Chief, Division of Thoracic Surgery, Istituto Nazionale Tumori, Fondazione Pascale, IRCCS, Naples, Italy

Alan D. L. Sihoe
Clinical Associate Professor, Department of Surgery, The University of Hong Kong
Chief of Thoracic Surgery, The University of Hong Kong Shenzhen Hospital
Guest Professor, Department of Thoracic Surgery, Tongji University Shanghai Pulmonary Hospital

Diego Gonzalez-Rivas, MD, FECTS
Director Uniportal VATS training program, Shanghai Pulmonary Hospital
Department of Thoracic Surgery and Lung Transplantation Coruña University Hospital and Minimally Invasive Thoracic Surgery Unit (UCTMI), Coruña, Spain

Editors

Yaxing Shen
Division of Thoracic Surgery, Zhongshan Hospital of Fudan University, Shanghai, China

Zhirui Zhou
Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Associate Editors

Wenzhao Zhong
Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China.

Yi Pan
Department of Radiation Oncology, Guangdong General Hospital, Guangzhou, China

Wenjie Cai
Associate chief physician of Department of Radiotherapy Oncology, First Hospital of Quanzhou, Affiliated to Fujian Medical University, Quanzhou, China.

Guiping Yu
Department of Cardiothoracic Surgery, The Affiliated Jiangyin Hospital of Southeast University Medical College, Jiangyin, China

Authors

Filippo Alongi
Radiation Oncology Department, Sacro Cuore-Don Calabria Hospital, 37024 Negrar Verona, Italy

Nicolaus Andratschke
Department of Radiation Oncology, University Hospital Zurich, Zürich, Switzerland

Nicolaus H. Andratschke
Department of Radiation Oncology, University Hospital Zurich, 8091 Zurich, Switzerland

Javier Aragón
Department of thoracic surgery, Asturias University Central Hospital, Asturias, Spain

Todd F. Atwood
University of California San Diego, 3855 Health Sciences Drive #0843, La Jolla, CA 92093, USA

José Belderbos
Department of Radiation Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Derek P. Bergsma
Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Luca Bertolaccini
Thoracic Surgery Unit, Sacro Cuore-Don Calabria Hospital, 37024 Negrar Verona, Italy

Andrea Bezjak
Radiation Medicine Program, Princess Margaret Hospital, Toronto, Ontario, Canada; Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada

Shilpa Bhatia
Department of Radiation Oncology, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO 80045, USA

Judit Boda-Heggemann
Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

Joe Y. Chang
Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Yuhchyau Chen
Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, USA

Allan Y. Chen
Department of Radiation Oncology, The Permanente Medical Group, Sacramento, CA, USA

Michelle B. Chen
Radiation Oncology, City of Hope Medical Center, Duarte, CA, USA

Yi-Jen Chen
Radiation Oncology, City of Hope Medical Center, Duarte, CA, USA

Hanbo Chen
Department of Radiation Oncology, London Regional Cancer Program, Western University, London, ON, Canada

Yuhchyau Chen
Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Steven W. Davis
Department of Radiation Medicine and Applied Sciences, San Diego School of Medicine, University of California, San Diego, USA

Sughosh Dhakal
Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Jay F. Dorsey
Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, USA

Neil Duggar
Department of Radiation Oncology, University of Mississippi Medical Center, Jackson, MS, USA

Katharina Fleckenstein
Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

Anian Frauenfeld
Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

Erin F. Gillespie
University of California San Diego, 3855 Health Sciences Drive #0843, La Jolla, CA 92093, USA

Shankar P. Giri
Department of Radiation Oncology, University of Mississippi Medical Center, Jackson, MS, USA

Meredith Elana Giuliani
Radiation Medicine Program, Princess Margaret Hospital, Toronto, Ontario, Canada; Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada

María Teresa Gómez-Hernández
Thoracic Surgery Service, Salamanca University Hospital and Salamanca's Bio-sanitary Institute (IBSAL), Salamanca, Spain

Diego Gonzalez-Rivas
Department of thoracic surgery at Coruña University Hospital and Minimally Invasive Thoracic Surgery Unit (UCTMI), Coruña, Spain

Matthias Guckenberger
Department of Radiation Oncology, University Hospital Wuerzburg, Wuerzburg, Germany; Department of Radiation Oncology, University Hospital Zurich, 8091 Zurich, Switzerland

Mary Z. Hare
Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, USA

Neil Joyce
Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, USA

Madhava R. Kanakamedala
Department of Radiation Oncology, University of Mississippi Medical Center, Jackson, MS, USA

Sana D. Karam
Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO 80045, USA

Brian D. Kavanagh
Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO 80045, USA

Frank J. Lagerwaard
Department of Radiation Oncology, VU University medical center, Amsterdam, the Netherlands

Percy Lee
Department of Radiation Oncology, University of California, Los Angeles, CA 90095, USA

Frank Lohr
Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

Billy W. Loo Jr
Radiation Oncology and Thoracic Radiation Oncology Program, Department of Radiation Oncology, Stanford University and Cancer Institute, Stanford, CA, USA

Alexander V. Louie
Department of Radiation Oncology, London Regional Cancer Program, Western University, London, ON, Canada

Thomas Lundquist
Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, USA

Michael T. Milano
Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, USA

René-Olivier Mirimanoff
Department of Radiation Oncology, Clinique de La Source, Lausanne CH-1004, Switzerland

Ursula Nestle
Department of Radiation Oncology, University Medical Center Freiburg, Freiburg, Germany; German Cancer Consortium (DKTK), Heidelberg (partner site Freiburg), Germany

Carsten Nieder
Department of Oncology and Palliative Medicine, Nordland Hospital, 8092 Bodø, Norway; Institute of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, 9038 Tromsø, Norway

Yoshihito Nomoto
Department of Radiology, Mie University School of Medicine, Tsu, Japan

Satoru Ochiai
Department of Radiation Oncology, Matsusaka Central Hospital, Matsusaka, Japan

David A. Palma
Department of Radiation Oncology, London Regional Cancer Program, London, Ontario, Canada

Itzell Perez
Department of thoracic surgery, Asturias University Central Hospital, Asturias, Spain

Douglas A. Rahn III
Department of Radiation Medicine and Applied Sciences, San Diego School of Medicine, University of California, San Diego, USA

Francesco Ricchetti
Radiation Oncology Department, Sacro Cuore-Don Calabria Hospital, 37024 Negrar Verona, Italy

Johannes Roesch
Department of Radiation Oncology, University Hospital Zurich, Zürich, Switzerland

Doug Rosenzweig
Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Chad G. Rusthoven
Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO 80045, USA

Jean-Claude M. Rwigema
Department of Radiation Oncology, University of California, Los Angeles, CA 90095, USA

Ajay P. Sandhu
Department of Radiation Medicine and Applied Sciences, San Diego School of Medicine, University of California, San Diego, USA

Michael C. Schell
Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, USA

Ugur Selek
Department of Radiation Oncology, Koç University, School of Medicine, Istanbul, Turkey; Department of Radiation Oncology, University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Suresh Senan
Department of Radiation Oncology, VU University medical center, Amsterdam, the Netherlands

Sashendra Senthi
William Buckland Radiotherapy Centre, The Alfred, Melbourne, Victoria, Australia

Anna O. Simeonova
Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

Charles B. Simone II
Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, USA

Deepinder Singh
Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, USA

Therese Smudzin
Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Table of Contents

Controversy and Debate

Future Direction

Stereotactic ablative radiotherapy for stage I NSCLC: recent advances and controversies

Suresh Senan[1], David A. Palma[2], Frank J. Lagerwaard[1]

[1]Department of Radiation Oncology, VU University Medical Center, Amsterdam, the Netherlands; [2]Department of Radiation Oncology, London Regional Cancer Program, London, Ontario, Canada

Correspondence to: Suresh Senan, MD. Department of Radiation Oncology, VU University Medical Center, De Boelelaan 1117, Postbox 7057, 1007 MB Amsterdam, The Netherlands. Email: s.senan@vumc.nl.

Abstract: Stereotactic ablative radiotherapy (SABR) is a technique that has rapidly entered routine care for early-stage peripheral non-small cell lung cancer in many countries in the last decade. The adoption of SABR was partly stimulated by advances in the so-called 'image guided' radiotherapy delivery. In the last 2 years, a growing body of publications has reported on clinical outcomes, acute and late radiological changes after SABR, and sub-acute and late toxicity. The local control rates in many publications have exceeded 90% when tumors of up to 5 cm have been treated, with corresponding regional nodal failure rates of approximately 10%. However, these results are not universal: lower control rates reported by some authors serve to emphasize the importance of quality assurance in all steps of SABR treatment planning and delivery. High-grade toxicity is uncommon when so-called 'risk-adapted' fractionation schemes are applied; an approach which involves the use of lower daily doses and more fractions when critical normal organs are in the proximity of the tumor volume. This review will address the new data available on a number of controversial topics such as the treatment of patients without a tissue diagnosis of malignancy, data on SABR outcomes in patients with severe chronic obstructive airways disease, use of a classification system for late radiological changes post-SABR, late treatment-related toxicity, and the evidence to support a need for expert multi-disciplinary teams in the follow-up of such patients.

Keywords: Non-small cell lung cancer; stage I; stereotactic ablative radiotherapy

Submitted Apr 22, 2011. Accepted for publication May 17, 2011.
doi: 10.3978/j.issn.2072-1439.2011.05.03
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2011.05.03

Introduction

Stereotactic ablative radiotherapy (SABR) is a form of high-precision radiotherapy delivery, which is characterized by an individualized approach to account for tumor mobility and accurate and reproducible patient setup prior to daily treatments (1,2). The results of SABR for early-stage non-small cell lung cancer (NSCLC) arguably represent one of most significant breakthroughs in curative therapy of lung cancer in the past two decades. SABR for pulmonary tumors is typically delivered in 3-8 daily fractions, resulting in good patient compliance and efficient resource utilization. Key features of SABR are summarized in *Figure 1*. The use of multiple non-coplanar radiation beams or volumetric modulated arcs results in highly conformal dose distributions, with rapid dose falloff in surrounding normal tissues. A typical dose distribution is shown in *Figure 2*, illustrating very high doses delivered to the target, with steep dose gradients and low doses to normal tissues.

Update on clinical outcomes

Outcomes of two prospective, single-arm multicenter trials in Europe and North America revealed 3-year local control rates ranging from 92-97% (3,4). A meta-analysis of observational studies of SABR reported a 5-year overall survival after SABR that is significantly higher (42%) than the 20% achieved with conventional radiotherapy (5). No randomized studies comparing the two treatments have been reported, but SABR for early-stage lung tumors has nevertheless gained wide acceptance in countries such as Japan (6), The Netherlands (7) and United States (8). More

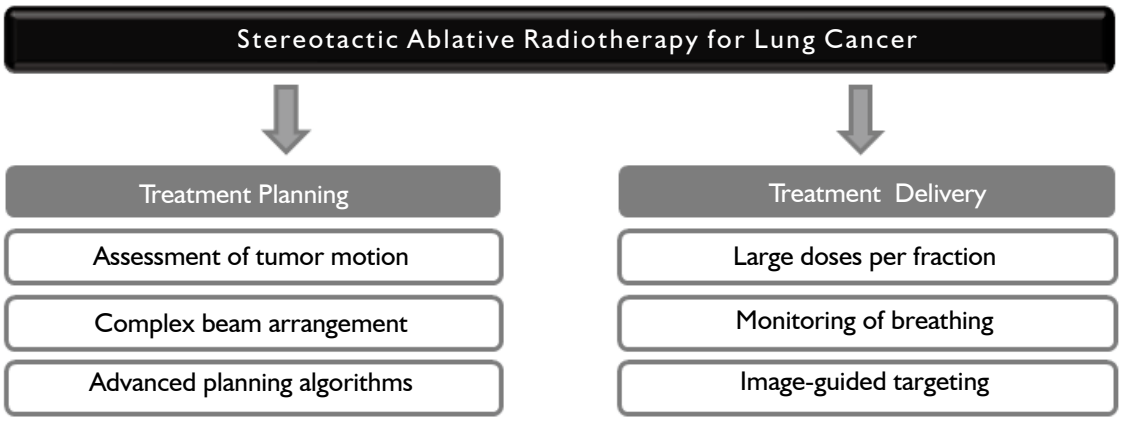


Figure 1 Key features of stereotactic ablative radiotherapy (SABR).

compelling evidence comes from a population-based cancer registry study of the impact of introducing SABR in a Dutch province, which revealed both an increase in radiotherapy utilization and improvement in median survival of elderly patients following the implementation of SABR (7). Excellent clinical outcomes have also been reported in elderly patients with co-existent severe chronic obstructive airways disease (COPD) (9), and a Markov model analysis predicted superior overall and quality-adjusted survival at 5 years in patients with all grades of severity of COPD after SABR versus no treatment (10).

It should be noted, however, that these results have been achieved in the context of rigorous quality control. The introduction of SABR in The Netherlands occurred in the setting of a pre-existing modern radiotherapy infrastructure, together with the introduction of quality assurance programs (11,12). Similarly, much of the available literature on SABR outcomes was derived from treatment of smaller tumors, and data on outcomes of SABR in larger and more centrally-located tumors is still relatively limited (13,14). However, SABR for treatment of central tumors using a 'risk-adapted' dose-fractionation schedule of 7.5 Gy (to a total dose of 60 Gy) reported high-rates of local control and a low incidence of sub-acute toxicity (15).

The issue of whether the excellent results of SABR for lung tumors can also be achieved when patients are treated outside pioneering academic institutions remains a pertinent one. Not all studies have achieved high rates of local control: one center reported an 2-year infield progression free probability of 65% (16), with a 1-year local progression-free survival of less than 80% for lesions measuring more than 4 cm (17). Similarly, other investigators have reported a 2-year local control rate of 70% for T2 tumors (18). Possible explanations for these higher local failure rates are failure to use 4-dimensional CT scans for planning, the limitation of RECIST criteria for assessment of local control, as well as prescribing doses to the tumor isocenter, rather than to the periphery of the target. Centers that prescribe doses to the center of the tumor volume deliver a substantially lower tumor dose than is the case where dose is prescribed to the tumor periphery (*Figure 3*), an approach which can compromise local control as biological effective doses of more than 100 Gy (BED_{10Gy}) are required for high local control rates (19).

Update on clinical toxicity

A recent review summarized the commoner SABR-related toxicities, which include radiation pneumonitis, bronchial stenosis or necrosis, rib fractures, esophageal injury or injuries to the brachial plexus (13). Only updated results of the more common toxicities, namely chest wall pain and radiation pneumonitis, will be addressed in this current update.

Severe chest wall pain has been reported in approximately 1-2% of patients, with rates of rib fractures ranging from 3-21% in reports evaluating relatively small numbers of patients (13,20). Risk factors for developing chest wall pain are treatment volume and distance from the tumor to the chest wall. Improved planning techniques are now available to reduce chest wall volumes receiving doses in excess of 30 Gy (21). However, the reported incidence of chest wall toxicity may increase in future as increasingly larger lung tumors are now being treated using SABR (14).

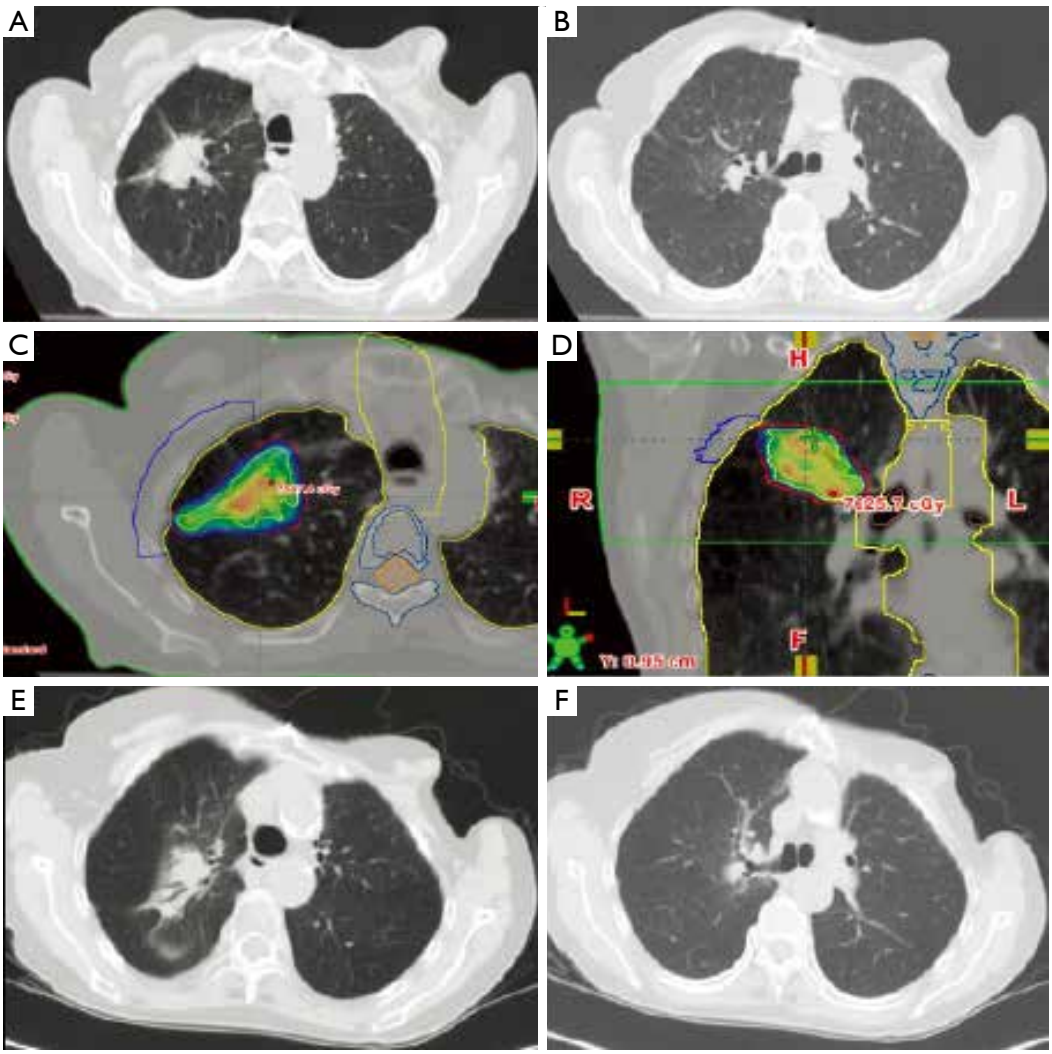


Figure 2 Images of a patient who developed a T2N0M0 adenocarcinoma in the right upper lobe, 30 years after surgery and radiotherapy for a left-sided breast cancer. The lung tumor was treated using SABR in 8-fractions of 7.5 Gy. Pre-treatment images (A,B), the high-dose region receiving 60 Gy in colorwash (C,D), and the post-treatment images at 8 months (E,F) are shown. No evidence for disease progression was observed at two- and-a-half years after SABR.

Nevertheless, chest wall toxicity post-SABR occurs less frequently than post-thoracotomy pain syndromes, which can manifest in about half of surgical patients (22). Up to 30% of post-surgical patients may continue to experience pain after 4 to 5 years (23), although the more widespread use of video-assisted thoracic surgery appears to have reduced this complication (24).

SABR delivery without a pathological diagnosis

In patients who undergo surgery for a growing, peripheral lung nodule suspicious for a lung cancer, a preoperative diagnosis is not always obtained, despite the known morbidity and mortality accompanying a surgical resection (25). For example, a large Japanese study on 1755 operated patients reported that 26% had no preoperative diagnosis (26). The problem of a lack of pre-treatment histological diagnosis is greater in medically inoperable patients who may be at higher risk for complications following a transthoracic needle biopsy. The probability of malignancy in a pulmonary nodule can be calculated using a combination of clinical, radiological and PET findings (27,28).

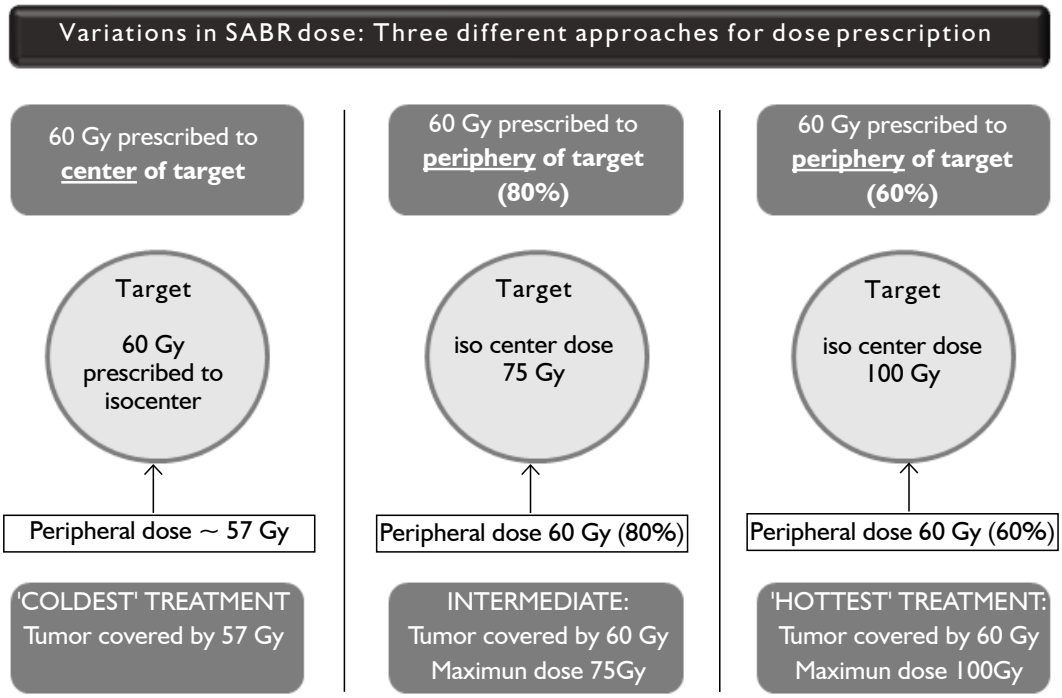


Figure 3 Different approaches described in the literature for dose prescription in SABR.

A number of investigators worldwide have described outcomes after SABR in patients without a pathological diagnosis (3,15,29). With such an approach, the risk of inadvertently treating benign nodules is largely dependent upon the prevalence of benign disease in the population. Current Dutch national radiotherapy guidelines allow for patients without pathology to be accepted for SABR in patients who fulfill all of the following (i) a new or growing lesion on CT scans with characteristics of malignancy; (ii) a high clinical risk for developing lung cancer and (iii) a FDG-PET positive lesion. This approach is based on data showing a benign diagnosis in less than 4.5% of Dutch patients who underwent surgery after a diagnosis of lung cancer was made based upon CT- and FDG-PET scans (30,31,32). The policy adopted in the Netherlands is consistent with guidelines of the American College of Chest Physicians, which recommends that a likelihood of malignancy that exceeds 60% warrants treatment without further diagnostic procedures (33). A recent population analysis indicated that inclusion of patients without a histological diagnosis could not have accounted for improvements in survival in an elderly population, as such patients had a poorer survival than patients with histological diagnosis (7).

Nevertheless, the abovementioned approach may be inappropriate in patients living in a region where infections, such as histoplasmosis, can give a false-positive PET uptake (34), thus reducing the specificity of PET. Another study from the United States reported that since institution of routine PET scans for lung nodules, nearly one third of resected nodules were found to be granulomas (35). With the availability of an effective second treatment alternative for patients with a clinical stage I NSCLC, it is clear that more effort should be directed towards obtaining a pathological diagnosis before initiating therapy.

Use of SABR in patients who are fit to undergo surgery

Nearly a third of patients presenting with early-stage disease do not undergo surgery (2). The changing demographics of lung cancer have led to this diagnosis being increasing made in elderly patients in whom the mortality associated with surgery ranges from 5.2-7.4% (25,36). The excellent outcomes of SABR in frail elderly patients has challenged the assumption that surgery should be the preferred treatment for all potentially operable patients with Stage I NSCLC (7,37), and these findings are supported by outcomes from

matched comparisons of SABR versus surgery (38,39). SABR is increasingly being performed in potentially operable patients who have fewer co-morbidities (40). A Markov model analysis of outcomes after either SABR or lobectomy for Stage I NSCLC for a 5-year time frame indicated that SABR may offer comparable overall survival and quality-adjusted life expectancy as compared with surgical resection (41). Two single-arm phase II trials of SABR in patients who are fit to undergo surgery have been completed, and the mature results of JCOG 0403 (NCT00238875) and RTOG 0618 (NCT00551369) are awaited. Well-powered prospective studies comparing surgery *vs.* SABR in early-stage lung cancer are warranted to further investigate the relative survival, quality of life, and cost characteristics of both treatment paradigms.

SABR and lymph node metastases

The rate of regional lymph node failure after SABR has been a question of substantial research interest, since the lymph nodes are not surgically staged. It is well-recognized that some patients with stage I NSCLC will have occult nodal disease not detectable by pre-operative staging: in a study of 715 patients with clinically-staged stage I disease who proceeded to resection, 16% were found to have occult N1 or N2 disease (34). Despite this, rates of regional failure after SABR are low in PET-staged patients, reported as 10% or less in most studies, comparable to regional recurrence rates after lobectomy (13). For example, a 4% regional recurrence rate was reported after SABR versus 18% after wedge resection (38). The question of why regional recurrence rates are lower than expected after SABR is unanswered, but several plausible hypotheses exist. During SABR, regional lymph nodes near the high-dose volume receive incidental radiation, and as such tumor cells in these nodes may be sterilized (38). In addition, immune activity may play a role: SABR substantially increases T-cell responses in the draining lymphatic tissues in mice, and these T-cell responses have strong anti-cancer cytotoxic activity; this effect is not seen after standard low-dose fractionated radiotherapy (42). Although further research is needed to elucidate these relationships, it remains that regional recurrence rates after SABR are low, even without pathologic staging of the regional nodes.

Patients with occult N1-N2 disease detected at surgery may be offered adjuvant chemotherapy, and SABR does not allow for the identification of such patients. Approximately 66% of patients who are candidates for adjuvant chemotherapy after surgery actually receive chemotherapy (43), and in such patients, adjuvant cisplatin-based chemotherapy is associated with a 5.4% overall survival benefit at 5-years (44). However, this survival improvement is quickly diluted: for a cohort of 100 patients with stage I NSCLC undergoing resection, approximately 16 will have N1/N2 disease, of which 10 would receive chemotherapy, and 0.5 extra patients would be alive after 5 years. Clearly, undertaking nodal dissection for the purposes of identifying chemotherapy candidates is unlikely to offer appreciable improvements in survival. Furthermore, data from patients aged ≥75 who have undergone a resection suggests that the survival in such patients is inferior to untreated controls when adjuvant chemotherapy is administered (45).

Follow-up after SABR

It is important to distinguish treatment-induced changes from disease progression in order to avoid both the risk of invasive diagnostic procedures or inappropriate salvage therapy (46). The application of RECIST criteria for evaluation of local response can be difficult because of frequent tumor fibrosis in the high-dose area of SABR (*Figure 4*). Most studies therefore, have reported local control as an absence of local progression, which can also be challenging. Moderate to intense FDG uptake observed shortly following SABR does not necessarily indicate a residual tumour (47,48).

Consequently, the evaluation of such changes by an experienced multi-disciplinary team of radiation oncologists, radiologists, nuclear medicine physicians and pulmonologists is essential in such a situation. Considerable experience is required to interpret radiological findings post-SABR, and reliable assessment becomes more essential now that increasingly fitter patients are primarily treated with SABR; many of these patients will be long-term survivors. Adequate follow-up imaging allows timely restaging and salvage treatment for local and regional recurrences, and also the detection and treatment of second malignancies that present at a rate of 2-3% per year in this patient population (49,50,51). We recommend re-assessment at 3-, 6- and 12-months after treatment, and every 6-12 months thereafter, with history, physical examination, and CT imaging.

Salvage surgical resections have now been reported in post-SABR recurrences, which were characterized by a rapid enlargement of a mass within a relatively short period (52,53). The role of surgical salvage as a treatment

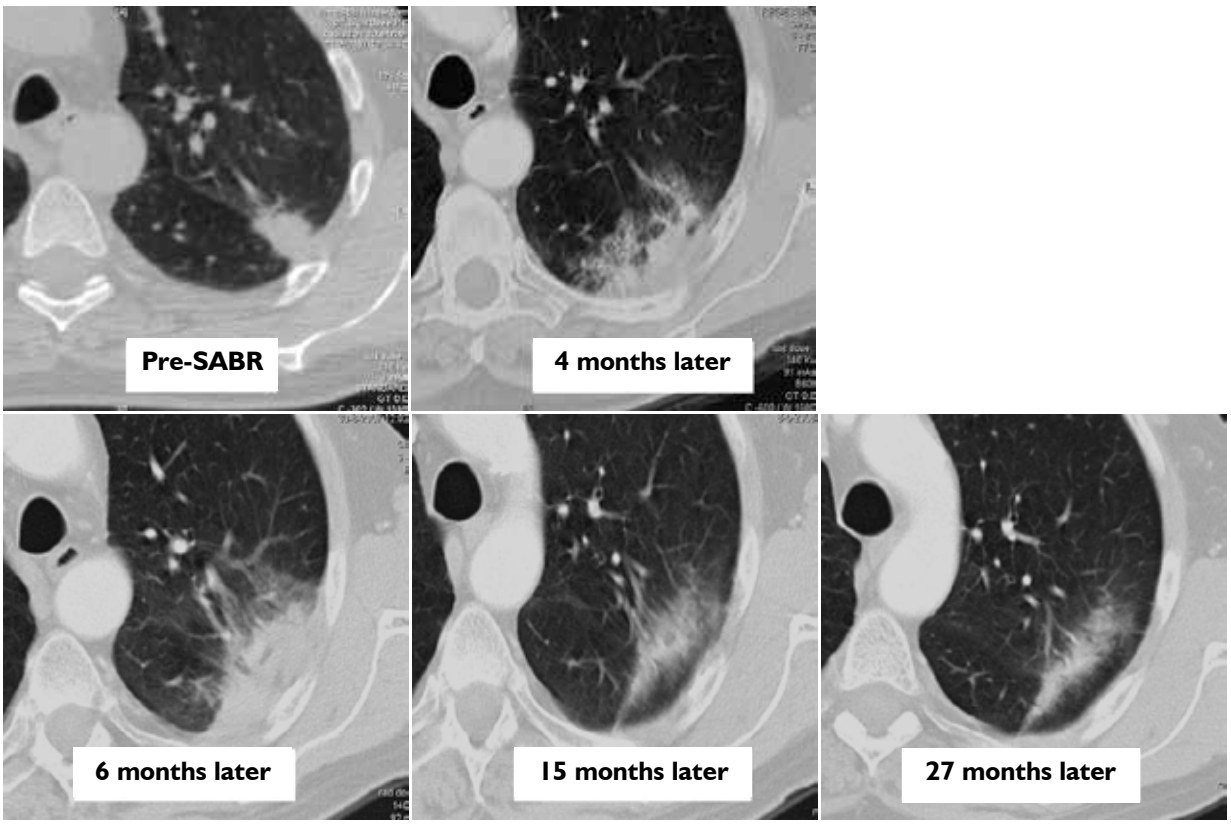


Figure 4 Serial imaging following SABR for a stage I non-small cell lung cancer. The focal radiological changes observed until 6 months were scored as 'patchy consolidation', while the late changes at 15 and 27 months were consistent with the score 'modified conventional' (*Table 1*).

Table 1 A scoring system for acute and late CT changes after stereotactic ablative radiotherapy (SABR) for early stage lung cancer. Standardized classifications will allow for ease of comparisons between different radiotherapy techniques and institutions (modified from reference 46)

Acute CT changes (≤6 months)		Late CT changes (>6 months)	
	Description		Description
Diffuse consolidation	Consolidation >5 cm in largest dimension. The involved region contains more consolidation than aerated lung.	Modified conventional pattern	Consolidation, loss of volume, bron-chiectasis similar to conventional radiation fibrosis, but usually less extensive. May be associated with GGO.
Patchy consolidation	Consolidation ≤5 cm in largest dimension and/or the involved region contains less consolidation than aerated lung	Mass-like	Well-circumscribed focal consolidation limited to area surrounding the tumor. The abnormality must be larger than the original tumor size
Diffuse GGO	>5 cm of GGO, (without consolidation). The involved region contains more GGO than normal lung	Scar-like	Linear opacity in the region of the tumor, associated with loss of volume
Patchy GGO	≤5 cm of GGO, (without consolidation), and/or the involved region contains less GGO than normal lung	No evidence of increased density	No new abnormalities. Includes patients with tumors that are stable, regressing or resolved, or fibrosis in the position of the original tumor that is not larger than the original tumor

GGO, ground glass opacifications.

option for recurrences post-SABR is a clinical scenario that will require further study, particularly as it may increase the preference for SABR in some patients who are fit to undergo primary surgery.

References

1. CJA Haasbeek, S Senan, EF Smit, MA Paul, BJ Slotman, FJ Lagerwaard. Critical Review of Non-Surgical Treatment Options for Stage I Non-Small Cell Lung Cancer. Oncologist 2008;13:309-19.
2. Palma D, Senan S. Stereotactic radiation therapy: changing treatment paradigms for stage I non-small cell lung cancer. Curr Opin Oncol 2011;23:133-9.
3. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.
4. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
5. Grutters JPC, Kessels AGH, Pijls-Johannesma M, De Ruysscher D, Joore MA, Lambin P. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: A meta-analysis. Radiother Oncol 2010;95:32-40.
6. Nagata Y, Hiraoka M, Mizowaki T, Narita Y, Matsuo Y, Norihisa Y, et al. Survey of stereotactic body radiation therapy in Japan by the Japan 3-D conformal external beam radiotherapy group. Int J Radiat Oncol Biol Phys 2009;75:343-7.
7. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. The impact of introducing stereotactic lung radiotherapy for elderly patients with Stage I NSCLC: A population-based time-trend analysis. J Clin Oncol 2010;28:5153-9.
8. Pan H, Simpson DR, Mell LK, Mundt AJ, Lawson JD. A survey of stereotactic body radiotherapy use in the United States. Cancer. 2011 Mar 15. doi: 10.1002/cncr.26067. [Epub ahead of print]
9. Palma D, Lagerwaard FJ, Rodrigues G, Haasbeek CJA, Senan S. Curative treatment of stage I non-small cell lung cancer in patients with severe COPD: Outcomes after stereotactic radiotherapy and systematic review of the literature. Int J Radiat Oncol Biol Phys. Forthcoming.
10. Louie AV, Rodrigues G, Hannouf M, Lagerwaard FJ, Palma D, Zaric GS, et al. Withholding Stereotactic Radiotherapy in Elderly Patients with Stage I Non-small Cell Lung Cancer and Co-existing COPD is not Justified: Outcomes of a Markov Model Analysis. Radiother Oncol. Forthcoming.
11. Hurkmans CW, Cuijpers JP, Lagerwaard FJ, Widder J, van der Heide UA, Schuring DD, et al. Recommendations for implementing stereotactic radiotherapy in peripheral stage IA non-small cell lung cancer: Report from the Quality Assurance Working Party of the randomized phase III ROSEL study. Radiat Oncol 2009 4:1.
12. Hurkmans CW, van Lieshout M, Schuring D, van Heumen MJT, Cuijpers JP, Lagerwaard FJ, et al. Quality assurance of 4D-CT scan techniques in a multicenter phase III trial of surgery versus stereotactic radiotherapy (ROSEL). Int J Radiat Oncol Biol Phys Oct 13. [Epub ahead of print]
13. Chi A, Liao Z, Nguyen NP, Xu J, Stea B, Komaki R. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: clinical implications. Radiother Oncol 2010;94:1-11.
14. Ong CL, Palma D, Verbakel WFAR, Slotman BJ, Senan S. Treatment of large stage I-II lung tumors using stereotactic body radiotherapy: Planning considerations and early toxicity. Radiother Oncol 2010;97:431-6.
15. Lagerwaard FJ, Haasbeek CJA, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2008;70:685-92.
16. Bral S, Van Parijs H, Soete G, Linthout N, Van Moorter L, Verellen D, et al. A feasibility study of image-guided hypofractionated conformal arc therapy for inoperable patients with localized non-small cell lung cancer. Radiother Oncol 2007;84:252-6.
17. Bral S, Gevaert T, Linthout N, Versmessen H, Collen C, Engels B, et al. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: Results of a Phase II trial. Int J Radiat Oncol Biol Phys. 2010 Aug 12. [Epub ahead of print]
18. Dunlap NE, Larner JM, Read PW, Kozower BD, Lau CL, Sheng K, et al. Size matters: a comparison of T1 and T2 peripheral non-small-cell lung cancers treated with stereotactic body radiation therapy (SBRT). J Thorac Cardiovasc Surg 2010;140:583-9.
19. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer:

updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100.
20. Stephans KL, Djemil T, Tendulkar RD, Robinson CG, Reddy CA, Videtic GM. Prediction of Chest Wall Toxicity From Lung Stereotactic Body Radiotherapy (SBRT). Int J Radiat Oncol Biol Phys 2011 Feb 5. [Epub ahead of print]
21. Ong CL, Verbakel WFAR, Cuijpers JP, Slotman BJ, Lagerwaard FJ, Senan S. Stereotactic radiotherapy for peripheral lung tumors: A comparison of volumetric modulated arc therapy and 3 other delivery approaches. Radiother Oncol 2010;97:437-42.
22. Rogers ML, Duffy JP. Surgical aspects of chronic post-thoracotomy pain. Eur J Cardiothorac Surg 2000;18:711-6.
23. Karmakar MK, Ho AM. Postthoracotomy pain syndrome. Thorac Surg Clin 2004;14:345-52.
24. Sugiura H, Morikawa T, Kaji M, Sasamura Y, Kondo S, Katoh H. Long-term benefits for the quality of life after video-assisted thoracoscopic lobectomy in patients with lung cancer. Surg Laparosc Endosc Percutan Tech 1999;9:403-8.
25. Finlayson E, Fan Z, Birkmeyer JD. Outcomes in octogenarians undergoing high-risk cancer operation: a national study. J Am Coll Surg 2007;205:729-34.
26. Sato S, Koike T, Yamato Y, Yoshiya K, Motono N, Takeshige M, et al. Diagnostic yield of preoperative computed tomography imaging and the importance of a clinical decision for lung cancer surgery. Gen Thorac Cardiovasc Surg 2010;58:461-6.
27. Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. Arch Intern Med 1997;157:849-855.
28. Herder GJ, van Tinteren H, Golding RP, Kostense PJ, Comans EF, Smit EF, et al. Clinical prediction model to characterize pulmonary nodules: validation and added value of 18F-fluorodeoxyglucose positron emission tomography. Chest 2005;128:2490-6.
29. Inoue T, Shimizu S, Onimaru R, Takeda A, Onishi H, Nagata Y, et al. Clinical outcomes of stereotactic body radiotherapy for small lung lesions clinically diagnosed as primary lung cancer on radiologic examination. Int J Radiat Oncol Biol Phys 2009;75:683-7.
30. van Tinteren H, Hoekstra OS, Smit EF, van den Bergh JH, Schreurs AJ, Stallaert RA, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. Lancet 2002;359:1388-93.
31. Herder GJ, Kramer H, Hoekstra OS, Smit EF, Pruim J, van Tinteren H, et al. Traditional versus up-front [18F] fluorodeoxyglucose-positron emission tomography staging of non-small-cell lung cancer: a Dutch cooperative randomized study. J Clin Oncol 2006;24:1800-6.
32. Belgers EH, Siebenga J, Bosch AM, van Haren EH, Bollen EC. Complete video-assisted thoracoscopic surgery lobectomy and its learning curve. A single center study introducing the technique in The Netherlands. Interact Cardiovasc Thorac Surg 2010;10:176-80.
33. Scott WJ, Howington J, Feigenberg S, Movsas B, Pisters K; American College of Chest Physicians. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:s234-42.
34. Cerfolio RJ, Bryant AS. Survival of patients with true pathologic stage I non-small cell lung cancer. Ann Thorac Surg 2009;88:917-22.
35. May BJ, Levsky JM, Godelman A, Jain VR, Little BP, Mahadevia PS, et al. Should CT Play a Greater Role in Preventing the Resection of Granulomas in the Era of PET? AJR Am J Roentgenol 2011;196:795-800.
36. Wouters MW, Siesling S, Jansen-Landheer ML, Elferink MA, Belderbos J, Coebergh JW, et al. Variation in treatment and outcome in patients with non-small cell lung cancer by region, hospital type and volume in the Netherlands. Eur J Surg Oncol 2010;36:s83-92.
37. Haasbeek CJA, Lagerwaard FJ, Antonisse ME, Slotman BJ, Senan S. Stage I non-small cell lung cancer in patients aged 75 years and older: Outcomes after stereotactic radiotherapy. Cancer 2010;116:406-14.
38. Grills IS, Mangona VS, Welsh R, Chmielewski G, McInerney E, Martin S, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol 2010;28:928-35.
39. Crabtree TD, Denlinger CE, Meyers BF, El Naqa I, Zoole J, Krupnick AS, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2010;140:377-86.
40. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Stereotactic body radiotherapy (SBRT) for operable Stage I non-small-cell lung cancer: Can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys. 2010 Jul 15. [Epub ahead of print]
41. Louie AV, Rodrigues G, Hannouf M, Zaric GS, Palma DA, Cao JQ, et al. Stereotactic body radiotherapy versus surgery for medically operable Stage I non-small-cell lung cancer: A Markov model-based decision analysis. Int J

Radiat Oncol Biol Phys. 2010 Oct 5. [Epub ahead of print]
42. Lee Y, Auh SL, Wang Y, Burnette B, Wang Y, Meng Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood 2009;114:589-95.
43. Felip E, Rosell R, Maestre JA, Rodríguez-Paniagua JM, Morán T, Astudillo J, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol 2010;28:3138-45.
44. NSCLC Meta-analyses Collaborative Group, Arriagada R, Auperin A, Burdett S, Higgins JP, Johnson DH, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010;375:1267-77.
45. Pepe C, Hasan B, Winton TL, Seymour L, Graham B, Livingston RB, et al. Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. J Clin Oncol 2007;25:1553-61.
46. Dahele M, Palma D, Lagerwaard F, Slotman B, Senan S. Radiological changes following stereotactic radiotherapy for stage I lung cancer. J Thorac Oncol. Forthcoming.
47. Matsuo Y, Nakamoto Y, Nagata Y, Shibuya K, Takayama K, Norihisa Y, et al. Characterization of FDG-PET images after stereotactic body radiation therapy for lung cancer. Radiother Oncol 2010;97:200-4.
48. Henderson MA, Hoopes DJ, Fletcher JW, Lin PF, Tann M, Yiannoutsos CT, et al. A pilot trial of serial 18F-fluorodeoxyglucose positron emission tomography in patients with medically inoperable stage I non-small-cell lung cancer treated with hypofractionated stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2010;76:789-95.
49. Pasini F, Verlato G, Durante E, de Manzoni G, Valduga F, Accordini S, et al. Persistent excess mortality from lung cancer in patients with stage I non-small-cell lung cancer, disease-free after 5 years. Br J Cancer 2003;88:1666-8.
50. Maeda R, Yoshida J, Ishii G, Aokage K, Hishida T, Nishimura M, et al. Long-term outcome and late recurrence in patients with completely resected stage IA non-small cell lung cancer. J Thorac Oncol 2010;5:1246-50.
51. Murthy SC, Reznik SI, Ogwudu UC, Farver CF, Arrossi A, Batizy LH, et al. Winning the battle, losing the war: the noncurative "curative" resection for stage I adenocarcinoma of the lung. Ann Thorac Surg 2010;90:1067-74.
52. Neri S, Takahashi Y, Terashi T, Hamakawa H, Tomii K, Katakami N, et al. Surgical treatment of local recurrence after stereotactic body radiotherapy for primary and metastatic lung cancers. J Thorac Oncol 2010;5:2003-7.
53. Chen F, Matsuo Y, Yoshizawa A, Sato T, Sakai H, Bando T, et al. Salvage lung resection for non-small cell lung cancer after stereotactic body radiotherapy in initially operable patients. J Thorac Oncol 2010;5:1999-2002.

Cite this article as: Senan S, Palma DA, Lagerwaard FJ. Stereotactic ablative radiotherapy for stage I NSCLC: recent advances and controversies. J Thorac Dis 2011;3(3):189-196. doi: 10.3978/j.issn.2072-1439.2011.05.03

Current Evidence

What is the current status of stereotactic body radiotherapy for stage I non-small cell lung cancer?

Matthias Guckenberger

Department of Radiation Oncology, University Hospital Wuerzburg, Wuerzburg, Germany
Correspondence to: Matthias Guckenberger, MD. Department of Radiation Oncology, University Hospital Wuerzburg, Josef-Schneider Strasse 11, 97080 Wuerzburg, Germany. Email: Guckenberger_m@klinik.uni-wuerzburg.de.

Submitted Jun 14, 2011. Accepted for publication Jun 15, 2011.
doi: 10.3978/j.issn.2072-1439.2011.06.04
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2011.06.04

Non-small cell lung cancer, if detected at early stage, is a disease with high probability for cure. However, the treatment in clinical practice is highly dependent on the co-morbidities of the patient, the performance status and age. A relevant proportion especially of the elderly patient population remains untreated despite the dismal prognosis of untreated stage I NSCLC with 5-year cancer specific survival (CSS) of only 16% (1,2). Conventionally fractionated radiotherapy has been the treatment of choice for medically inoperable patients: however, outcome is suboptimal with 5-year CSS ranging between 13% and 39% (3); most importantly, local disease recurrence is the most frequent site of failure, not systemic metastases (4). CSS is excellent after lobectomy ranging between 100% and 57.6% depending on the size of the primary tumor (5). Despite a randomized trial demonstrated inferior outcome of sublobar resection compared to lobectomy (6), sublobar resection is practiced especially in high-risk patients aiming at preservation of pulmonary function (7). Wedge resection seems to be insufficient even for small tumors whereas segmentectomy results in promising CSS if the tumor size is below 3 cm (5,8).

Stereotactic body radiotherapy (SBRT)—or stereotactic ablative radiotherapy, which are different names for identical treatment methodologies—has gained much attention as a novel and promising treatment option for early stage NSCLC. The rational for the practice of SBRT is the finding that very high radiation doses are required to locally control NSCLC, higher than achievable with conventional radiation techniques (9): SBRT allows treatment with these escalated irradiation doses to the site of the primary tumor by optimal lung sparing using modern radiotherapy technologies, e.g., breathing motion compensation and image-guidance. As a consequence, local tumor control after SBRT is substantially better compared to conventionally fractionated radiotherapy: in a large number of prospective phase II trials, local tumor control ranged consistently between 84–98% (10-14) compared to only 60% after conventional radiotherapy (3). This translates into CSS rates between 72.5% and 88% after 3 years (10,11,13).

The review in this issue of the *Journal of Thoracic Disease* summarizes the current status of SBRT (15). No randomized controlled trial tested SBRT in comparison with any other treatment modality: best-supportive care, conventionally fractionated radiotherapy, sublobar resection or lobectomy. However, there is a growing body of evidence based on prospective phase II trials and well performed retrospective analyses, which define the current status of SBRT in this wide spectrum of patients with early stage NSCLC.

A recent population based analysis demonstrated that the introduction of SBRT significantly decreased the proportion of untreated patients older than 75 years, which resulted in significantly improved overall survival (2): a non-invasive treatment practiced in an out-patient fashion with only 1–8 treatment fractions is a low barrier for patients and referring doctors to choose a curative treatment approach. Even very poor pulmonary function in the context of severe COPD should not be considered as contraindication for SBRT (16,17).

The difference in both local tumor control and CSS between SBRT and conventional radiotherapy is highly consistent in the literature and is considered as so large, that SBRT is widely accepted as the treatment of choice

for patients who are no candidates for surgical resection. Overall survival now seems to be influenced mainly by the comorbidities of the patients (18). As stated clearly in the review, strict and comprehensive quality assurance covering indication for SBRT, staging, treatment planning, radiotherapy delivery and follow-up—the whole chain of SBRT treatment—are mandatory for the practice of this sophisticated treatment. Such quality assurance protocols are published and broadly available, which will be the basis for a broader clinical implementation of SBRT outside of highly specialist academical centres.

There is limited data comparing SBRT and surgical treatments. A retrospective study reported improved local tumor control and regional control with no difference in CSS for SBRT compared to wedge resection (19). Japanese patients, who were operable but refused surgery, experienced excellent 5 year overall survival of 72% and 62% for stage IA and IB after SBRT, respectively; these results are approaching overall survival after lobectomy, which is also indicated by a Markov-Model analysis (20). In the absence of randomized trials for both SBRT and sublobar resection, both SBRT and sublobar resection should be offered to high-risk patient as viable treatment options. For patient suitable for lobectomy, SBRT offers a curative treatment option if surgery is refused.

References

1. Raz DJ, Zell JA, Ou SH, Gandara DR, Anton-Culver H, Jablons DM. Natural history of stage I non-small cell lung cancer: implications for early detection. Chest 2007;132:193-9.
2. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: A population-based time-trend analysis. J Clin Oncol 2010;28:5153-9.
3. Rowell NP, Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable). Cochrane Database Syst Rev 2001:CD002935.
4. Sibley GS, Jamieson TA, Marks LB, Anscher MS, Prosnitz LR. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. Int J Radiat Oncol Biol Phys 1998;40:149-54.
5. Okada M, Nishio W, Sakamoto T, Uchino K, Yuki T, Nakagawa A, et al. Effect of tumor size on prognosis in patients with non-small cell lung cancer: the role of segmentectomy as a type of lesser resection. J Thorac Cardiovasc Surg 2005;129:87-93.
6. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
7. Blasberg JD, Pass HI, Donington JS. Sublobar resection: a movement from the Lung Cancer Study Group. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer 2010;5:1583-93.
8. Kates M, Swanson S, Wisnivesky JP. Survival following lobectomy and limited resection for the treatment of stage I non-small cell lung cancer<=1 cm in size: a review of SEER data. Chest 2011;139:491-6.
9. Partridge M, Ramos M, Sardaro A, Brada M. Dose escalation for non-small cell lung cancer: Analysis and modelling of published literature. Radiother Oncol 2011;99:6-11.
10. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.
11. Fakiris AJ, McGarry RC, Yiannoutsos CT, Papiez L, Williams M, Henderson MA, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75:677-82.
12. Bral S, Gevaert T, Linthout N, Versmessen H, Collen C, Engels B, et al. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: Results of a phase II trial. Int J Radiat Oncol Biol Phys 2010 Aug 12. [Epub ahead of print]
13. Ricardi U, Filippi AR, Guarneri A, Giglioli FR, Ciammella P, Franco P, et al. Stereotactic body radiation therapy for early stage non-small cell lung cancer: results of a prospective trial. Lung Cancer 2010;68:72-7.
14. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
15. Senan S, Palma DA, Lagerwaard FJ. Stereotactic ablative radiotherapy for stage I NSCLC: Recentadvances and controversies. J Thorac Dis 2011;3:189-96.
16. Stephans KL, Djemil T, Reddy CA, Gajdos SM, Kolar M, Machuzak M, et al. Comprehensive analysis of pulmonary function test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. J Thorac Oncol 2009;4:838-44.

17. Palma D, Lagerwaard F, Rodrigues G, Haasbeek C, Senan S. Curative treatment of stage I non-small-cell lung cancer in patients with severe COPD: Stereotactic radiotherapy outcomes and systematic review. Int J Radiat Oncol Biol Phys. 2011 Jun 1. [Epub ahead of print]
18. Kopek N, Paludan M, Petersen J, Hansen AT, Grau C, Høyer M. Co-morbidity index predicts for mortality after stereotactic body radiotherapy for medically inoperable early-stage non-small cell lung cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2009;93:402-7.
19. Grills IS, Mangona VS, Welsh R, Chmielewski G, McInerney E, Martin S, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol 2010;28:928-35.
20. Louie AV, Rodrigues G, Hannouf M, Zaric GS, Palma DA, Cao JQ, et al. Stereotactic body radiotherapy versus surgery for medically operable stage I non-small-cell lung cancer: A markov model-based decision analysis. Int J Radiat Oncol Biol Phys. 2010 Oct 5. [Epub ahead of print]

Cite this article as: Guckenberger M. What is the current status of stereotactic body radiotherapy for stage I non-small cell lung cancer? J Thorac Dis 2011;3(3):147-149. doi: 10.3978/j.issn.2072-1439.2011.06.04

Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer

Javier Aragón[1], Itzell Perez[1], Diego Gonzalez-Rivas[2]

[1]Department of Thoracic Surgery, Asturias University Central Hospital, Asturias, Spain; [2]Department of Thoracic Surgery at Coruña University Hospital and Minimally Invasive Thoracic Surgery Unit (UCTMI), Coruña, Spain

Correspondence to: Javier Aragón, MD. Department of Thoracic Surgery, Asturias University Central Hospital, Calle Carretera de Rubín, s/n, 33011 Oviedo, Asturias Oviedo, Spain. Email: javieraragon241064@gmail.com.

Submitted Jun 28, 2015. Accepted for publication Jun 28, 2015.
doi: 10.3978/j.issn.2072-1439.2015.07.04
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.07.04

With great interest we read the study of Hamaji *et al.* (1) entitled "*Video-Assisted Thoracoscopic lobectomy Versus Stereotactic Radiotherapy for Stage I Lung Cancer*" which was recently published in *Annals of Thoracic Surgery*. With a mean follow-up of 48 months, the authors show that lobectomy performed by video-assisted thoracoscopic surgery (VATS) offers better results than stereotactic radiotherapy (SBRT) in the treatment of patients with pathologically proved non-small cell lung cancer (NSCLC) in early stages.

Nowadays and according to current guidelines the surgery is the best therapeutic option for the treatment of early stages NSCLC (2-4); being the inoperability secondary to the high surgical risk the SBRT main indication. However, they have shown comparable results with VATS/SBRT in retrospective studies with matching cases (5) including studies with patients who were medically operable but refused surgery (6).

The study has been conducted exclusively in patients with NSCLC stage I and IIa potentially resectable who met adequate standards of operability. The paper attempts to analyze if the SBRT can be an elective valid therapeutic option comparable with the surgery and not as alternative when the patient's general conditions pose an unacceptable surgical risk. Theoretically the SBRT can provide many advantages to the patients: it's a treatment that doesn't require hospitalization, preserves more the lung function, could shortened waiting times and recovery of daily life, and the satisfaction degree and acceptance of the patient is greater. It can be especially useful in older patients who often tend to refuse surgery and who are more difficult to cooperate with postoperative rehabilitation measures.

Although at work the VATS group results are clearly better in both overall survival and cause specified as the recurrence rates, we consider the probability of lymph node involvement, not objectified in the SBRT group, could be adversely affected the results in this treatment group.

This is particularly important especially considering that different pathological strains are included, and some of them have specially propensity for lymphatic spread. For that reason it may be useful for futures studies include a systematic lymph node biopsy by endobronchial ultrasound (EBUS).

We have observed that in the VATS group they included some patients who had undergone chemotherapy, so it's difficult to know what is the impact of this factor about the results of this specific group of the study.

Similarly, the fact of the close monitoring of SBRT group was based on a TAC realization while in the VATS group was based on a simple physical examination, makes us think which could be underestimated the recurrence time in the operated patients.

As is the case with sublobar resections, it is difficult to compete with the anatomical lobar resection for obtaining good long-term results. Perhaps the SBRT is the ideal alternative to such resections and could support on similar inclusion criteria.

Acknowledgements

None.

Footnote

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

References

1. Hamaji M, Chen F, Matsuo Y, et al. Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer. Ann Thorac Surg 2015;99:1122-9.
2. Vansteenkiste J, De Ruysscher D, Eberhardt WE, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi89-98.
3. Ettinger DS, Wood DE, Akerley W, et al. Non-small cell lung cancer, version 6.2015. J Natl Compr Canc Netw 2015;13:515-24.
4. Detterbeck FC, Lewis SZ, Diekemper R, et al. Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2013;143:7S-37S.
5. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 2013;24:1543-8.
6. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352-8.

Cite this article as: Aragón J, Perez I, Gonzalez-Rivas D. Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer. J Thorac Dis 2015;7(7):1074-1075. doi: 10.3978/j.issn.2072-1439.2015.07.04

SBRT in operable early stage lung cancer patients

Johannes Roesch, Nicolaus Andratschke, Matthias Guckenberger

Department of Radiation Oncology, University Hospital Zurich, Zürich, Switzerland

Correspondence to: Johannes Roesch. UniversitätsSpital Zürich, Klinik für Radio-Onkologie, Rämistr. 100, CH-8091, Zürich, Switzerland. Email: Johannes.Roesch@usz.ch.

Abstract: Since decades the gold standard for treatment of early stage non-small cell lung cancer (NSCLC) is surgical lobectomy plus mediastinal lymph node dissection. Patients in worse health status are treated with sublobar resection or radiation treatment. With development of stereotactic-body-radiotherapy (SBRT), outcome of patients treated with radiation was substantially improved. Comparison of SBRT and surgical techniques is difficult due to the lack of randomized trials. However, all available evidence in form of case control studies of population based studies show equivalence between sublobar resection and SBRT indicating that SBRT—when performed by a trained and experienced team—should be offered to all high-risk surgical patients. For patients not willing to take the risk of lobectomy and therefore refusing surgery, SBRT is an excellent treatment option.

Keywords: Stereotactic-body-radiotherapy (SBRT); surgical resection; early stage non-small cell lung cancer (NSCLC)

Submitted Aug 07, 2014. Accepted for publication Aug 12, 2014.
doi: 10.3978/j.issn.2218-6751.2014.08.06
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2014.08.06

Background

Malignant neoplasm of the lung is the most frequent cause of cancer related death in males and second in females.

Early stage non-small cell lung cancer (NSCLC) is cured in many cases by local treatment. Unfortunately three quarters of NSCLC cases are detected in a later stage of disease due to a lack of clinical symptoms. Cure is then only achieved in few patients. However, the combination of population aging and oncoming CT-based screenings programs will increase the number of diagnosed early stage lung cancer especially in the elderly patients (1,2).

In the past, surgical lobectomy plus mediastinal lymph node dissection was established as the standard treatment in operable patients. Patients with higher surgical risk due to comorbidity may undergo sublobar resection, although its outcome is inferior based on a randomized study (3). About 80% of stage I disease patients undergo surgical resection (4). However in treatment of elderly patients with increasing numbers of comorbidities, the value of surgery will decrease (5). In the USA the percentage of patients with age >85 years as well as having >3 comorbidities doubled between 1998 and 2007. The number of patients treated with no local therapy at all increased from 14.6% in 1998 to 18.3% in 2007. Looking at these data the decline in use of surgical resection from 75.2% to 67.3%, despite the increasing use of less invasive (6) video-assisted thoracoscopic surgery (VATS), isn't surprising (7). According to data from the Netherlands this proportion even drops <40% in patients >75 years (8). Best supportive care without curative treatment intention is practiced with increasing frequency. Vest *et al.* report of a growing proportion not receiving a curative local treatment from 14.6% in 1998 to 18.3% in 2007 in the USA (7). This number increases in patients >75 years up to 26% (9). Five-year cancer-specific-survival is about 14% (10) in patients undergoing best supportive care indicating the need for a curative and simultaneously minimally or non-invasive treatment option.

For inoperable patients so-called conventional radiation treatment is an established curative treatment option. Conventional radiation in this context usually means applying 60-66 Gy in 2 Gy-fractions over a time period of 6-7 weeks. Overall survival (OS) of about 30% and cancer specific survival (CSS) of about 50% after 3 years

can be achieved in these non-operable patient cohorts (11). However, retrospective studies showed local tumor relapse being the most frequent site of treatment failure and proofed a correlation of dose escalation and OS (12-15).

During the last years improved results were achieved in non-operable patients by introduction of novel radiotherapy concepts and technologies: stereotactic-body-radiotherapy (SBRT). SBRT combines several modern technologies to accurately treat tumors with very high irradiation doses. These irradiation doses are delivered in few radiotherapy fractions or even in one radiosurgical session. Safety of this radical but non-invasive treatment is achieved by confinement of high irradiation doses to the tumor and sparing of healthy normal tissue.

History

SBRT evolved from cranial stereotactic radiotherapy (SRT) by transferring its principles and practice to extracranial sites. Pioneer work done in the mid-1990s at the Karolinska Hospital in Sweden and this concept was quickly adopted and further developed in Japan and Germany (16-19).

Stereotaxy started out as a form of neurosurgery that uses a mechanical head frame and a precise 3-dimensional (3D) coordinate system to align and direct surgical instruments. This combination of a rigid frame and a constitutive 3D-coordinate system was used in radio-oncology for better patient-fixation and treatment planning. With improvement and development of modern imaging systems the coordinates could be referred to the imaging data-sets and non-invasive fixation systems replaced rigid frames. This opened the path for stereotactic radiation therapy to target extracranial tumor sites.

Definition of SBRT

Several work groups have given their version of a definition of SBRT (20-24). A consensus can be described as followed: SBRT is a method of external beam radiotherapy (EBRT) that accurately delivers a high dose of irradiation in one or few treatment fractions to an image-defined extracranial target. Shifting from conventional RT to SBRT is not only a simple modification of techniques, but should be considered as a complete replacement of concepts. More precise methods in terms of localizing and tracking the tumor, fixation of the patient, planning techniques and application of radiotherapy itself, are needed to apply hypo-fractionated doses as used in SBRT. However, by applying the SBRT-concept the whole diagnosis and treatment work flow and not only technical issues have to be adapted (20).

Clinical outcome of SBRT

SBRT in non-operable patients

Conventional radiation therapy has been proven to provide better outcome than best supportive care (25) and was therefore considered to be the first-line therapy in non-operable early stage lung cancer patients. Some years ago this changed in favor of SBRT. NCCN Guidelines as well as the ESMO Clinical Practice Guidelines consider SBRT as first line treatment in medically inoperable patients (26,27).

It's an attractive treatment option for several reasons: non-invasive, outpatient-basis and short overall treatment time of 1-2 weeks.

Compared to best supportive care

Population-based analyses from the Netherlands (8,28) and the US (29) demonstrated an improvement in OS for stage I NSCLC in elderly patients by introducing SBRT.

Haasbeek showed that OS improved in patients treated with radiotherapy by introducing SBRT from 16 months to 24 months between 2001 and 2009 in the Netherlands (8). Palma *et al*. showed a corresponding increase from 16 months to 21 months in elderly patients in North Holland, regardless of treatment modality (28). Furthermore both showed that availability of SBRT reduced the proportion of patients receiving non-curative treatment by 7-12%. Simultaneously, the proportion of patients that underwent surgery remained constant.

The US study is based on the SEER database of patients older than 65 years and compared five different treatment options for patients with stage I NSCLC (29): best supportive care, conventional radiotherapy, SBRT, sublobar resection and lobectomy. Propensity score matching between SBRT and non-SBRT treatment was performed to correct for imbalances of race, sex, education level, median income, comorbidity score, histology, tumor grade, tumor size, and presence of lymph node sampling. SBRT achieved improved OS compared to best supportive care and conventional radiotherapy and differences were not significant compared to sublobar resection and lobectomy.

Compared to conventionally fractionated radiotherapy

Several prospective phase II trials have been conducted

Table 1 Summary of retrospective (n>200) and prospective trials evaluating SBRT-outcomes

Study	Year	No. of cases	Fractionation	Tox. grade pneumonitis/rib fracture [%]	OS 3a (%)	CSS 3a (%)	LC 3a (%)	Median follow up
Retrospective								
Onishi (30)	2004	245		≥2 [6.5/0.8]	56	78	86.5	24
Onishi (31)	2007	257		≥2 [5.4/1.6]	56.8	76.9	86	38
Grills SBRT (32)	2012	505		≥3 [2/1]	48	77	91	30
Senthi (33)	2013	676			55 [2a]	–	95 [2a]	33
Guckenberger (34)	2013	582		≥2 [7/4]	49		80	21
Prospective								
Nagata (35)	2005	45	4×12 Gy (at isocenter)	>3 [0]	72 (stage IB)	–	98	30
Baumann (36)	2009	57	3×15 Gy (67% isodose)	≥3 [29.8]	60	88	92	35
Fakiris (37)	2009	70	60-66 Gy in 3 fractions (80% Isodose)	≥3 [15.7]	42.7	81.7	88.1	50
Timmerman (38,39)	2009	55	3×18 Gy	≥3 [16.3]	55.8	–	97.6	34
Bral (40)	2011	40	60 Gy in 3-4 fractions	≥3 [20]	52 [2a]	64 [2a]	84 [2a]	16
Ricardi (41)	2010	62	3×15 Gy (80% isodose)	≥3 [3.2/1.6]	57.1	72.5	87.8	28

SBRT, stereotactic-body-radiotherapy; OS, overall survival; CSS, cause-specific survival; LC, local control; 3a, 3-year-value; 2a, 2-year-value.

and 2-3 years local tumor control and OS ranged between 84-98% and 43-72%, respectively.

Prospective trials (see *Table 1*) showed 2-3 years local tumor-control rates of 84-98% and OS between 43-72% in non-operable patients suffering from early-stage NSCLC and treated with SBRT (24,35-37,41,42). Even though different SBRT methodologies were used the results were similar and highly consistent.

As better local tumor control was shown to go along with higher OS in patients treated with conventional radiation therapy (12-15), it can also be shown that even further improvement of local control (LC) by applying SBRT transfers into even better OS (29). In a meta-analysis done by Grutters *et al*., 2-year OS for SBRT was 70% *vs*. 53% for CRT and 2-year CSS was 83% *vs*. 67% (43).

Large retrospective analyses confirmed the good results described above in clinical practice outside of prospective clinical trials. Only studies with >200 patients are included in *Table 1*, which summarizes a total of 2,265 cases. The outcome of 582 patients treated at 13 German and Austrian centers was analyzed (34): it was shown that local tumor control and OS were independent from SBRT-technology used at different time periods and at different centers. Furthermore dose escalation was again shown as a significant factor influencing OS and LC. A biological effective dose BED of at least 106 Gy (2 Gy equivalent) resulted in a 3-year LC rate of 92.5% compared to 79.6% in all patients. three-year OS increased from 47.1% to 62.2%. This dose dependency of local failure was also seen by Onishi *et al*. They reported a cut-off-value at a BED =100 Gy leading to a 3-year OS of 88.9% compared with 69.4% in medically operable patients (30,31). The data collected by Grills *et al*. showed a better tumor control in patients treated with more than a BED of 105 Gy (32). A meta-analysis done by Zhang shows that the outcome gets worse for a BED below 83.2 Gy and a BED that exceeds 146 Gy. Therefore the favorable dose should be in between (44). OS is mainly affected by distant metastases and comorbidities. The probability of distant metastases is up to 20-26% of cases and is correlated to lesion size (33,38,45,46).

Numerous pro- and retrospective studies have confirmed good SBRT results. High consistency between the studies and reproducibility of results in clinical daily routine even in change of clinical setting can be seen. This is a strong indicator for quality and robustness of SBRT treatment.

Compared to radiofrequency ablation (RFA)

RFA alone (47) or in combination with conventional

radiotherapy (48) has been introduced as a minimally invasive option into the treatment of stage I NSCLC. No study performed a direct comparison between SBRT and RFA but a recent literature review reported improved local tumor control, CSS and OS after SBRT compared to RFA (49). Additionally, toxicity and 30-day mortality (50) were lower after SBRT resulting in the conclusion, that SBRT should be proposed as the first non-surgical treatment to high-risk patients.

SBRT in medically operable patients compared to surgery

First-line treatment in operable stage I NSCLC patients is surgery: lobectomy proved to achieve better outcome than wedge resection (51). Today sublobar anatomical resection (segmentectomy) is discussed as another option (52,53); whether segmentectomy delivers worse (3) or comparable outcome compared to lobectomy is still under investigation (54,55).

Based on the highly promising outcome of SBRT in medically inoperable patients, three randomized trials comparing SBRT with lobectomy (ROSEL, STAR) or sublobar resection (ACOSOG Z4099/RTOG 1021) (56) have been started but all three studies closed very early due to poor accrual: <5% of the planned patients were enrolled leaving us without level A evidence.

Hence level A evidence won't be available in the near future. Several studies compared SBRT to surgery using statistical methods like matched pair analyses and propensity score matching to correct for imbalances in patient characteristics.

Grills *et al*. performed a retrospective single-institution comparison between SBRT and wedge resection. Improved local tumor control in favor of SBRT (5% *vs*. 24%) with no differences in CSS was reported. OS was better in the surgical cohort, which was explained by older age and increased comorbidities in the SBRT patients (57). The previously cited US population based SEER analysis showed no difference in OS and CSS for SBRT versus sublobar resection or lobectomy after propensity score matching (29). Moreover SBRT was shown to be the treatment with best OS up to 6 months in the total of patients, showing its superiority in morbidity and treatment-related mortality.

Puri *et al*. reported identical CSS between SBRT and surgery (lobectomy in 80% of the patients) (58). OS appeared better after surgery compared to SBRT but was not statistically significant and this potential difference was explained by increased pulmonary comorbidities in the SBRT cohort, which was not corrected in the propensity score matching. Verstegen *et al*. compared SBRT and VATS lobectomy in 128 patients after propensity score matching of gender, age, clinical tumor stage, tumor diameter, location of the tumor, pretreatment tumor histology, lung function (FEV1%), Charlson comorbidity score and WHO performance score. Locoregional control was better after SBRT with no differences in freedom from progression and OS (59). A total of 257 propensity scored patients were analyzed by Crabtree *et al*. and there was again no difference seen between local recurrence, CSS or OS after 3 years (60).

Few studies reported outcome after SBRT when patients were considered suitable for surgical resection but surgery was actively refused by the patients. Two Japanese and one Dutch study described excellent OS of 70% after 5 years (n=87) (61), 86% after 3 years (n=29) (62) and 85% at 3 years (n=177) (63), respectively, results which compare well to OS after lobectomy. Uematsu reported a 3-year OS of 86% in medically operable patients (62). A Markov Model-based decision analysis was developed by Louie *et al*. comparing SBRT and lobectomy. They postulated a comparable OS and quality-adjusted life expectancy (64).

Palma *et al*. reported of comparable outcome in COPD patients undergoing surgical resection or SBRT. However 30-day mortality was significantly higher (0% *vs*. 10%) in surgical patients (65). This compares with a low 30-day mortality rate after SBRT in general (34). Grills *et al*. described no treatment-related death in a nonrandomized retrospective analysis comparing wedge resection with SBRT. Nevertheless a higher 30-day readmission rate in the wedge resection group was conspicuous (57).

Consequently, SBRT appears as a viable treatment option in the situation, when lobectomy is refused by the patients. Additionally, SBRT appears equivalent to sublobar resection and both options with their specific pros and cons should be discussed with the patient.

Toxicity and quality of live after lung SBRT

The majority of patients treated with SBRT suffer from severe pulmonary or cardiovascular comorbidities and their poor pulmonary status, which does not allow surgical resection. Consequently pulmonary toxicity is an important point of concern in lung SBRT. Radiation induced pneumonitis (RP) is usually seen after a median of 5 months which is longer compared to conventional radiotherapy (66). The treatment of peripherally located tumors <5 cm in diameter causes RP in below 10% of cases. Risk of RP is

reported to be dependent on planned target volume (PTV), mean lung dose and low-dose spread for conventional radiotherapy (67,68). The conclusion that risk factors are similar in SBRT is supported by several papers (66,69-73). RP grade ≥II ranges from below 10% in the majority of reports up to even 28% in one report (66,69,72-80). Development of high grade RP after stereotactic treatment is rarely reported. The two largest retrospective papers show an incidence of RP Tox. Grade ≥2 of below 8% (32,34). Patients with pre-existent pulmonary fibrosis might be at increased risk for RP.

Additionally, pulmonary function is stable after SBRT with a loss of <10% (FEV1, DLCO) within 24 months after treatment (81,82). Pulmonary toxicity was not increased even in patients with very poor pre-SBRT pulmonary function and with severe COPD GOLD III-IV (82). Bishawi *et al.* even postulated a better pulmonary function after four months from SBRT for non-COPD-patients because of tumor shrinkage (83).

Chest wall toxicity (myositis, neuralgia, rip fracture, subcutaneous fibrosis, and skin ulceration) has been reported when tumors are located close to the respective normal tissue structures. Doses >30 Gy (delivered in 3 fractions) to the chest wall haven been correlated with these toxicities and the volume of the chest wall exposed to these doses should be minimized by conformal treatment planning (61,84-90). Based on their data, Mutter *et al.* suggest a 30 Gy constraint to a max of 70 cm^3 of the chest wall (2 cm expansion of the lung) to prevent chest wall pain.

Severe toxicity to the brachial plexus (neuropathic pain, motor weakness, or sensory alteration), large bronchi (stenosis with pulmonary atelectasis) and esophagus (ulceration, perforation, fistula) has been reported but these toxicities are rare. Limiting the total dose to the plexus to <26 Gy in 3-4 fractions can minimize the risk of toxicity (91).

Whereas safety of such high single and total doses has been demonstrated for peripheral lung tumors of usually <5 cm size, higher rates of severe toxicity have been reported in centrally located tumors with critical organs like the esophagus and large bronchi close by (92,93). Occurrence of these toxicities is known from conventional radiotherapy to centrally located tumors and therefore not unforeseen (94).

Some reports even mention treatment-related deaths, especially in centrally located tumors (40,95). Senthi *et al.* reported of a treatment-related death rate of up to 2.7%, respectively of 1% if BED below 210 Gy is used. In contrast, safety of SBRT for centrally located tumors has been reported if the total dose is delivered using a larger number (5-10) of treatment fractions and a lower single-fraction dose (33). Considerable volume definition and avoidance of multiple treatments to the same hilar bronchus is recommended (96) in order to prevent central toxicities like major airway occlusion (97).

Studies consistently reported that SBRT has no detrimental or negative on quality-of-life (QoL) (98-100). Overall QoL as well as subdomains of dyspnea and cough were stable after SBRT in all studies and one study described significantly improved emotional functioning (98).

Clinical implemention of SBRT for early stage NSCLC

Before technical details of SBRT will be discussed, it is of fundamental importance that SBRT is practiced by a dedicated multidisciplinary team. All members of this team—radiation oncologists, medical physicists and radiation technologists—should receive specific training and gain experience in SBRT and treatment needs to follow written guidelines.

Several groups and organizations published their recommendation to best practice of SBRT and a short summary is given below.

Clinical evaluation

Evaluation of performance status and pulmonary function is necessary to enable a sensible treatment concept. In surgical series, higher perioperative morbidity and lower quality of life is correlated to higher age (>70 years) and the presence of other comorbidities (5,101,102). To get an impression of the patients risk to suffer from treatment-complications, pulmonary function testing like maximal oxygen uptake (VO_{2max}), forced expiratory volume in 1 second (FEV_1) or diffusion capacity (D_{CO}) is essential for both postoperative and post-radiation performance (102,103). Worse performance status and FEV_1 were proven to correlate with higher side effects in normo-fractioned radiation therapy (104).

Histo-pathological confirmation of lung cancer

Whenever possible and reasonable a biopsy for histopathological confirmation of the cancer diagnosis should be performed. However transbronchial biopsy or transthoracic fine needle aspiration is sometimes impossible

due to unacceptable risks or may fail to prove malignancy.

In this case clinical (age, smoking habit, history of prior malignancy) and radiological criteria (diameter, spiculation, nodule growth rate) are proven to be good prediction or risk factors for malignancy (105-112). The volume doubling time of malignant nodules is somewhere between 20-400 and most often around 120 days (113,114). Nodules, that grow faster or slower have a higher probability to be benign (111). In addition a PET-CT scan might help to evaluate the probability, as higher glucose metabolism is an indicator for malignancy (115).

Repeated imaging to evaluate the growth pattern is an option in patient with intermediate risk of malignancy. However, observation might put the patient at risk of disease progression (116). Although probability of tumor cell dissemination rises with stage of disease, even small primary pulmonary lesions are able to cause disseminated disease (117-120). Therefore the point of time when curative local treatment has the possibility to be successful might be missed.

If malignancy is highly likely based on the described criteria, immediate SBRT without histopathological confirmation is justified (121), as is in this population also standard practice in thoracic surgery (29,122).

As SBRT is also a way of curative treatment of unfit patients that would otherwise have gone to best supportive care, the percentage of histopathological confirmation is already decreasing as the risk for invasive confirmation might be too high (9).

Staging of disease

Correct disease staging is essential for treatment indication because only the primary tumor without elective nodal irradiation is treated in SBRT. Several working groups have given their recommendations referring to staging procedures prior to SBRT (20,21).

Chest-CT-scan using intravenous contrast including the upper abdomen is mandatory.

A whole body FDG-PET/CT-scan might not only improve the malignancy prediction model as mentioned earlier, but there's also evidence of increased detection accuracy of nodal and/or distant metastases (123-125). Even though this is still a subject of discussion for early stage lung cancer (126,127). A FDG-PET/CT scan as part of disease staging is widely postulated (20,21). Furthermore, a PET-CT scan serves to exclude clinically relevant distant metastases or second malignancies.

Pathological FDG uptake in mediastinal lymph nodes should lead to histopathological evaluation in order to prevent overstating (127). Endoscopic (EUS) or endobronchial ultrasound (EBUS) can be used for biopsy guidance. If the situation is still unclear, a mediastinoscopy may be necessary.

Interdisciplinary decision making

SBRT is a local modality that complements other surgical and non-surgical treatments.

As a corollary of this and the big efforts that are made to lay the foundation for high quality treatment, indication for SBRT should be discussed in a multidisciplinary tumor board to offer the patient a therapy concept, that's sensible, individualized and which ensures a high level of quality.

Treatment planning

Imaging for target volume and organ at risk (OAR) definition is a key factor for successful SBRT practice. Only macroscopic targets and small, immediately adjacent volumes of potential microscopic spread are treated in SBRT. 4D-imaging is essential to evaluated breathing induced tumor motion on a patient individual basis. Breathing induced target motion requires motion management strategies to minimize the dose delivered to non-pathological tissue. Several different approaches can be applied and have already been implemented into routine practice (128). In principle, we distinguish between passive 4D motion management strategies and active strategies, where treatment is adapted in real-time to breathing motion. Despite huge technical differences between the strategies, no difference in clinical outcome has been reported.

A minimum dose of at least 100 Gy BED in 3-8 fractions is mandatory as described above. In this context the importance of reassuring the delivery of the prescribed dose was shown by Latifi *et al*. They report of a higher recurrence rate for patients planned with Pencil-Beam compared to collapsed cone convolution (CCC)-algorithm even though the prescribed nominal dose and constraints were identical. This has been conducted to a relative dosimetric underdosing (129).

Patient immobilization and setup

Accurate target localization is essential to apply the conformal radiation dose to the target volume and to spare critical organs at risk. Strict immobilization by patient-

customized systems enable reproducible patient setup and reduce inter- and intrafraction motion of the patients' bony anatomy. To reduce uncertainties to a minimum, daily pretreatment imaging is an essential part of each and every treatment session.

Breathing induced target motion, setup-errors and baseline shifts must be taken into account. Image guidance can be achieved through both: visualization of the lung tumor directly or implanted fiducial markers that act as a surrogate for tumor position. Post- and/or mid-treatment imaging is recommended for quality assurance, particularly in single fraction SBRT.

Follow-up

To confirm and validate efficacy, outcomes and toxicities after SBRT, early and late effects have to be assiduous documented. Special attention has to be brought to potential complications. Differentiation between post-SBRT fibrosis and local recurrence of disease is sometimes difficult. Huang *et al*. published a systematic literature review and proposed an algorithm for this important clinical issue (130). Because of these difficulties, clinical and radiological follow-up should therefore be performed at the treating institution, where all detailed information about the SBRT treatment is available.

Summary

SBRT is an evidence-based and effective treatment option for patients with stage I NSCLC. Superiority to best supportive care and conventional radiotherapy has been documented in prospective and retrospective studies. Local tumor control rates exceeding 90% is consistently achieved and OS is mainly limited by comorbidities. Equivalence to surgery has been consistently reported in matched pair analysis and studies using propensity score matching but level A evidence is missing due to a lack of successfully completed randomized trials: a multi-professional team experienced and trained in SBRT and image guided radiotherapy is essential for safe practice. Discussion in multidisciplinary tumor boards considering the perioperative risk of the patient and patient's preference is important.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol 2009;27:2758-65.
2. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
3. Whitson BA, Groth SS, Andrade RS, et al. Survival after lobectomy versus segmentectomy for stage I non-small cell lung cancer: a population-based analysis. Ann Thorac Surg 2011;92:1943-50.
4. Raz DJ, Zell JA, Ou SH, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. Chest 2007;132:193-9.
5. de Perrot M, Licker M, Reymond MA, et al. Influence of age on operative mortality and long-term survival after lung resection for bronchogenic carcinoma. Eur Respir J 1999;14:419-22.
6. Port JL, Mirza FM, Lee PC, et al. Lobectomy in octogenarians with non-small cell lung cancer: ramifications of increasing life expectancy and the benefits of minimally invasive surgery. Ann Thorac Surg 2011;92:1951-7.
7. Vest MT, Herrin J, Soulos PR, et al. Use of new treatment modalities for non-small cell lung cancer care in the Medicare population. Chest 2013;143:429-35.
8. Haasbeek CJ, Palma D, Visser O, et al. Early-stage lung cancer in elderly patients: a population-based study of changes in treatment patterns and survival in the Netherlands. Ann Oncol 2012;23:2743-7.
9. Palma D, Visser O, Lagerwaard FJ, et al. Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery. Radiother Oncol 2011;101:240-4.
10. Detterbeck FC, Gibson CJ. Turning gray: the natural history of lung cancer over time. J Thorac Oncol 2008;3:781-92.
11. Chadha AS, Ganti AK, Sohi JS, et al. Survival in untreated early stage non-small cell lung cancer. Anticancer Res 2005;25:3517-20.
12. Rowell NP, Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable): a systematic review. Thorax 2001;56:628-38.
13. Martel MK, Ten Haken RK, Hazuka MB, et al. Estimation of tumor control probability model parameters from 3-D dose distributions of non-small cell lung cancer patients.

Lung Cancer 1999;24:31-7.
14. Partridge M, Ramos M, Sardaro A, et al. Dose escalation for non-small cell lung cancer: analysis and modelling of published literature. Radiother Oncol 2011;99:6-11.
15. Sibley GS, Jamieson TA, Marks LB, et al. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. Int J Radiat Oncol Biol Phys 1998;40:149-54.
16. Wulf J, Hädinger U, Oppitz U, et al. Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame. Radiother Oncol 2000;57:225-36.
17. Uematsu M, Shioda A, Tahara K, et al. Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience. Cancer 1998;82:1062-70.
18. Lax I, Blomgren H, Näslund I, et al. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. Acta Oncol 1994;33:677-83.
19. Herfarth KK, Debus J, Lohr F, et al. Extracranial stereotactic radiation therapy: set-up accuracy of patients treated for liver metastases. Int J Radiat Oncol Biol Phys 2000;46:329-35.
20. Guckenberger M, Andratschke N, Alheit H, et al. Definition of stereotactic body radiotherapy: principles and practice for the treatment of stage I non-small cell lung cancer. Strahlenther Onkol 2014;190:26-33.
21. Potters L, Kavanagh B, Galvin JM, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2010;76:326-32.
22. Kirkbride P, Cooper T. Stereotactic body radiotherapy. Guidelines for commissioners, providers and clinicians: a national report. Clin Oncol (R Coll Radiol) 2011;23:163-4.
23. Sahgal A, Roberge D, Schellenberg D, et al. The Canadian Association of Radiation Oncology scope of practice guidelines for lung, liver and spine stereotactic body radiotherapy. Clin Oncol (R Coll Radiol) 2012;24:629-39.
24. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys 2010;37:4078-101.
25. Wisnivesky JP, Halm E, Bonomi M, et al. Effectiveness of radiation therapy for elderly patients with unresected stage I and II non-small cell lung cancer. Am J Respir Crit Care Med 2010;181:264-9.
26. NCCN Clinical Practice Guidelines in Oncology: Non-small cell lung cancer Version 1.2013 [Internet]. Available online: http://www.nccn.org/
27. Vansteenkiste J, De Ruysscher D, Eberhardt WE, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi89-98.
28. Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. J Clin Oncol 2010;28:5153-9.
29. Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. Int J Radiat Oncol Biol Phys 2012;84:1060-70.
30. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004;101:1623-31.
31. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100.
32. Grills IS, Hope AJ, Guckenberger M, et al. A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy. J Thorac Oncol 2012;7:1382-93.
33. Senthi S, Haasbeek CJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol 2013;106:276-82.
34. Guckenberger M, Allgäuer M, Appold S, et al. Safety and efficacy of stereotactic body radiotherapy for stage 1 non-small-cell lung cancer in routine clinical practice: a patterns-of-care and outcome analysis. J Thorac Oncol 2013;8:1050-8.
35. Nagata Y, Takayama K, Matsuo Y, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys 2005;63:1427-31.
36. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.
37. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study.

Int J Radiat Oncol Biol Phys 2009;75:677-82.
38. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010,303:1070-6.
39. Timmerman RD, Paulus R, Galvin J, et al. Stereotactic Body Radiation Therapy for Medically Inoperable Early-stage Lung Cancer Patients: Analysis of RTOG 0236. IJROBP 2009,75:S3.
40. Bral S, Gevaert T, Linthout N, et al. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: results of a Phase II trial. Int J Radiat Oncol Biol Phys 2011;80:1343-9.
41. Ricardi U, Filippi AR, Guarneri A, et al. Stereotactic body radiation therapy for early stage non-small cell lung cancer: results of a prospective trial. Lung Cancer 2010;68:72-7.
42. Pennathur A, Luketich JD, Heron DE, et al. Stereotactic radiosurgery for the treatment of stage I non-small cell lung cancer in high-risk patients. J Thorac Cardiovasc Surg 2009;137:597-604.
43. Grutters JP, Kessels AG, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. Radiother Oncol 2010;95:32-40.
44. Zhang J, Yang F, Li B, et al. Which is the optimal biologically effective dose of stereotactic body radiotherapy for Stage I non-small-cell lung cancer? A meta-analysis. Int J Radiat Oncol Biol Phys 2011;81:e305-16.
45. Nath SK, Sandhu AP, Kim D, et al. Locoregional and distant failure following image-guided stereotactic body radiation for early-stage primary lung cancer. Radiother Oncol 2011;99:12-7.
46. Andratschke N, Zimmermann F, Boehm E, et al. Stereotactic radiotherapy of histologically proven inoperable stage I non-small cell lung cancer: patterns of failure. Radiother Oncol 2011;101:245-9.
47. Lanuti M, Sharma A, Willers H, et al. Radiofrequency ablation for stage I non-small cell lung cancer: management of locoregional recurrence. Ann Thorac Surg 2012;93:921-7; discussion 927-88.
48. Dupuy DE, DiPetrillo T, Gandhi S, et al. Radiofrequency ablation followed by conventional radiotherapy for medically inoperable stage I non-small cell lung cancer. Chest 2006;129:738-45.
49. Renaud S, Falcoz PE, Olland A, et al. Is radiofrequency ablation or stereotactic ablative radiotherapy the best treatment for radically treatable primary lung cancer unfit for surgery? Interact Cardiovasc Thorac Surg 2013;16:68-73.
50. Crabtree T, Puri V, Timmerman R, et al. Treatment of stage I lung cancer in high-risk and inoperable patients: comparison of prospective clinical trials using stereotactic body radiotherapy (RTOG 0236), sublobar resection (ACOSOG Z4032), and radiofrequency ablation (ACOSOG Z4033). J Thorac Cardiovasc Surg 2013;145:692-9.
51. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
52. Harada H, Okada M, Sakamoto T, et al. Functional advantage after radical segmentectomy versus lobectomy for lung cancer. Ann Thorac Surg 2005;80:2041-5.
53. Landreneau RJ, Normolle DP, Christie NA, et al. Recurrence and survival outcomes after anatomic segmentectomy versus lobectomy for clinical stage I non-small-cell lung cancer: a propensity-matched analysis. J Clin Oncol 2014;32:2449-55.
54. Okada M, Koike T, Higashiyama M, et al. Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study. J Thorac Cardiovasc Surg 2006;132:769-75.
55. Tsutani Y, Miyata Y, Nakayama H, et al. Oncologic outcomes of segmentectomy compared with lobectomy for clinical stage IA lung adenocarcinoma: propensity score-matched analysis in a multicenter study. J Thorac Cardiovasc Surg 2013;146:358-64.
56. Fernando HC, Timmerman R. American College of Surgeons Oncology Group Z4099/Radiation Therapy Oncology Group 1021: a randomized study of sublobar resection compared with stereotactic body radiotherapy for high-risk stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2012;144:S35-8.
57. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol 2010;28:928-35.
58. Puri V, Crabtree TD, Kymes S, et al. A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: a decision analysis. J Thorac Cardiovasc Surg 2012;143:428-36.
59. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 2013;24:1543-8.
60. Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2010;140:377-86.

61. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352-8.
62. Uematsu M, Shioda A, Suda A, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. Int J Radiat Oncol Biol Phys 2001;51:666-70.
63. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:348-53.
64. Louie AV, Rodrigues G, Hannouf M, et al. Stereotactic body radiotherapy versus surgery for medically operable Stage I non-small-cell lung cancer: a Markov model-based decision analysis. Int J Radiat Oncol Biol Phys 2011;81:964-73.
65. Palma D, Lagerwaard F, Rodrigues G, et al. Curative treatment of Stage I non-small-cell lung cancer in patients with severe COPD: stereotactic radiotherapy outcomes and systematic review. Int J Radiat Oncol Biol Phys 2012;82:1149-56.
66. Guckenberger M, Baier K, Polat B, et al. Dose-response relationship for radiation-induced pneumonitis after pulmonary stereotactic body radiotherapy. Radiother Oncol 2010;97:65-70.
67. Yorke ED, Jackson A, Rosenzweig KE, et al. Correlation of dosimetric factors and radiation pneumonitis for non-small-cell lung cancer patients in a recently completed dose escalation study. Int J Radiat Oncol Biol Phys 2005;63:672-82.
68. Seppenwoolde Y, Lebesque JV, de Jaeger K, et al. Comparing different NTCP models that predict the incidence of radiation pneumonitis. Normal tissue complication probability. Int J Radiat Oncol Biol Phys 2003;55:724-35.
69. Guckenberger M, Heilman K, Wulf J, et al. Pulmonary injury and tumor response after stereotactic body radiotherapy (SBRT): results of a serial follow-up CT study. Radiother Oncol 2007;85:435-42.
70. Matsuo Y, Shibuya K, Nakamura M, et al. Dose--volume metrics associated with radiation pneumonitis after stereotactic body radiation therapy for lung cancer. Int J Radiat Oncol Biol Phys 2012;83:e545-9.
71. Ong CL, Palma D, Verbakel WF, et al. Treatment of large stage I-II lung tumors using stereotactic body radiotherapy (SBRT): planning considerations and early toxicity. Radiother Oncol 2010;97:431-6.
72. Borst GR, Ishikawa M, Nijkamp J, et al. Radiation pneumonitis in patients treated for malignant pulmonary lesions with hypofractionated radiation therapy. Radiother Oncol 2009;91:307-13.
73. Barriger RB, Forquer JA, Brabham JG, et al. A dose-volume analysis of radiation pneumonitis in non-small cell lung cancer patients treated with stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2012;82:457-62.
74. Yamashita H, Nakagawa K, Nakamura N, et al. Exceptionally high incidence of symptomatic grade 2-5 radiation pneumonitis after stereotactic radiation therapy for lung tumors. Radiat Oncol 2007;2:21.
75. Hof H, Herfarth KK, Münter M, et al. Stereotactic single-dose radiotherapy of stage I non-small-cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 2003;56:335-41.
76. Nyman J, Johansson KA, Hultén U. Stereotactic hypofractionated radiotherapy for stage I non-small cell lung cancer--mature results for medically inoperable patients. Lung Cancer 2006;51:97-103.
77. Takayama K, Nagata Y, Negoro Y, et al. Treatment planning of stereotactic radiotherapy for solitary lung tumor. Int J Radiat Oncol Biol Phys 2005;61:1565-71.
78. Wulf J, Haedinger U, Oppitz U, et al. Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: a noninvasive treatment approach in medically inoperable patients. Int J Radiat Oncol Biol Phys 2004;60:186-96.
79. Gomez DR, Hunt MA, Jackson A, et al. Low rate of thoracic toxicity in palliative paraspinal single-fraction stereotactic body radiation therapy. Radiother Oncol 2009;93:414-8.
80. Prendergast BM, Dobelbower MC, Bonner JA, et al. Stereotactic body radiation therapy (SBRT) for lung malignancies: preliminary toxicity results using a flattening filter-free linear accelerator operating at 2400 monitor units per minute. Radiat Oncol 2013;8:273.
81. Guckenberger M, Kestin LL, Hope AJ, et al. Is there a lower limit of pretreatment pulmonary function for safe and effective stereotactic body radiotherapy for early-stage non-small cell lung cancer? J Thorac Oncol 2012;7:542-51.
82. Stephans KL, Djemil T, Reddy CA, et al. Comprehensive analysis of pulmonary function Test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. J Thorac Oncol 2009;4:838-44.
83. Bishawi M, Kim B, Moore WH, et al. Pulmonary function testing after stereotactic body radiotherapy to the lung. Int J Radiat Oncol Biol Phys 2012;82:e107-10.

84. Stephans KL, Djemil T, Tendulkar RD, et al. Prediction of chest wall toxicity from lung stereotactic body radiotherapy (SBRT). Int J Radiat Oncol Biol Phys 2012;82:974-80.
85. Dunlap NE, Cai J, Biedermann GB, et al. Chest wall volume receiving >30 Gy predicts risk of severe pain and/or rib fracture after lung stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2010;76:796-801.
86. Woody NM, Videtic GM, Stephans KL, et al. Predicting chest wall pain from lung stereotactic body radiotherapy for different fractionation schemes. Int J Radiat Oncol Biol Phys 2012;83:427-34.
87. Andolino DL, Forquer JA, Henderson MA, et al. Chest wall toxicity after stereotactic body radiotherapy for malignant lesions of the lung and liver. Int J Radiat Oncol Biol Phys 2011;80:692-7.
88. Mutter RW, Liu F, Abreu A, et al. Dose-volume parameters predict for the development of chest wall pain after stereotactic body radiation for lung cancer. Int J Radiat Oncol Biol Phys 2012;82:1783-90.
89. Creach KM, El Naqa I, Bradley JD, et al. Dosimetric predictors of chest wall pain after lung stereotactic body radiotherapy. Radiother Oncol 2012;104:23-7.
90. Pettersson N, Nyman J, Johansson KA. Radiation-induced rib fractures after hypofractionated stereotactic body radiation therapy of non-small cell lung cancer: a dose- and volume-response analysis. Radiother Oncol 2009;91:360-8.
91. Forquer JA, Fakiris AJ, Timmerman RD, et al. Brachial plexopathy from stereotactic body radiotherapy in early-stage NSCLC: dose-limiting toxicity in apical tumor sites. Radiother Oncol 2009;93:408-13.
92. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
93. Song SY, Choi W, Shin SS, et al. Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. Lung Cancer 2009;66:89-93.
94. Miller KL, Shafman TD, Anscher MS, et al. Bronchial stenosis: an underreported complication of high-dose external beam radiotherapy for lung cancer? Int J Radiat Oncol Biol Phys 2005;61:64-9.
95. Milano MT, Chen Y, Katz AW, et al. Central thoracic lesions treated with hypofractionated stereotactic body radiotherapy. Radiother Oncol 2009;91:301-6.
96. Oshiro Y, Aruga T, Tsuboi K, et al. Stereotactic body radiotherapy for lung tumors at the pulmonary hilum. Strahlenther Onkol 2010;186:274-9.
97. Joyner M, Salter BJ, Papanikolaou N, et al. Stereotactic body radiation therapy for centrally located lung lesions. Acta Oncol 2006;45:802-7.
98. van der Voort van Zyp NC, Prévost JB, van der Holt B, et al. Quality of life after stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2010;77:31-7.
99. Widder J, Postmus D, Ubbels JF, et al. Survival and quality of life after stereotactic or 3D-conformal radiotherapy for inoperable early-stage lung cancer. Int J Radiat Oncol Biol Phys 2011;81:e291-7.
100. Lagerwaard FJ, Aaronson NK, Gundy CM, et al. Patient-reported quality of life after stereotactic ablative radiotherapy for early-stage lung cancer. J Thorac Oncol 2012;7:1148-54.
101. Handy JR Jr, Asaph JW, Skokan L, et al. What happens to patients undergoing lung cancer surgery? Outcomes and quality of life before and after surgery. Chest 2002;122:21-30.
102. Bolliger CT, Wyser C, Roser H, et al. Lung scanning and exercise testing for the prediction of postoperative performance in lung resection candidates at increased risk for complications. Chest 1995;108:341-8.
103. Markos J, Mullan BP, Hillman DR, et al. Preoperative assessment as a predictor of mortality and morbidity after lung resection. Am Rev Respir Dis 1989;139:902-10.
104. Robnett TJ, Machtay M, Vines EF, et al. Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 20001;48:89-94.
105. Swensen SJ, Silverstein MD, Ilstrup DM, et al. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. Arch Intern Med 1997;157:849-55.
106. Herder GJ, Kramer H, Hoekstra OS, et al. Traditional versus up-front [18F] fluorodeoxyglucose-positron emission tomography staging of non-small-cell lung cancer: a Dutch cooperative randomized study. J Clin Oncol 2006;24:1800-6.
107. Midthun DE, Swensen SJ, Jett JR. Clinical strategies for solitary pulmonary nodule. Annu Rev Med 1992;43:195-208.
108. Henschke CI, Yankelevitz DF, Naidich DP, et al. CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. Radiology 2004;231:164-8.
109. Swensen SJ, Jett JR, Sloan JA, et al. Screening for lung cancer with low-dose spiral computed tomography. Am J Respir Crit Care Med 2002;165:508-13.

110. Quint LE, Park CH, Iannettoni MD. Solitary pulmonary nodules in patients with extrapulmonary neoplasms. Radiology 2000;217:257-61.
111. Patel VK, Naik SK, Naidich DP, et al. A practical algorithmic approach to the diagnosis and management of solitary pulmonary nodules: part 1: radiologic characteristics and imaging modalities. Chest 2013;143:825-39.
112. Patel VK, Naik SK, Naidich DP, et al. A practical algorithmic approach to the diagnosis and management of solitary pulmonary nodules: part 2: pretest probability and algorithm. Chest 2013;143:840-6.
113. Garland LH, Coulson W, Wollin E. The rate of growth and apparent duration of untreated primary bronchial carcinoma. Cancer 1963;16:694-707.
114. Friberg S, Mattson S. On the growth rates of human malignant tumors: implications for medical decision making. J Surg Oncol 1997;65:284-97.
115. Duhaylongsod FG, Lowe VJ, Patz EF Jr, et al. Lung tumor growth correlates with glucose metabolism measured by fluoride-18 fluorodeoxyglucose positron emission tomography. Ann Thorac Surg 1995;60:1348-52.
116. Murai T, Shibamoto Y, Baba F, et al. Progression of non-small-cell lung cancer during the interval before stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2012;82:463-7.
117. Patz EF Jr, Rossi S, Harpole DH Jr, et al. Correlation of tumor size and survival in patients with stage IA non-small cell lung cancer. Chest 2000;117:1568-71.
118. Pantel K, Izbicki J, Passlick B, et al. Frequency and prognostic significance of isolated tumour cells in bone marrow of patients with non-small-cell lung cancer without overt metastases. Lancet 1996;347:649-53.
119. Peck K, Sher YP, Shih JY, et al. Detection and quantitation of circulating cancer cells in the peripheral blood of lung cancer patients. Cancer Res 1998;58:2761-5.
120. Cote RJ, Beattie EJ, Chaiwun B, et al. Detection of occult bone marrow micrometastases in patients with operable lung carcinoma. Ann Surg 1995;222:415-23; discussion 423-5.
121. Verstegen NE, Lagerwaard FJ, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy following a clinical diagnosis of stage I NSCLC: comparison with a contemporaneous cohort with pathologically proven disease. Radiother Oncol 2011;101:250-4.
122. Sawada S, Yamashita M, Komori E, et al. Evaluation of resected tumors that were not diagnosed histologically but were suspected of lung cancer preoperatively: PD1-3-5. J Thorac Oncol 2007;2:S422.
123. Lardinois D, Weder W, Hany TF, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. N Engl J Med 2003;348:2500-7.
124. Aquino SL, Asmuth JC, Alpert NM, et al. Improved radiologic staging of lung cancer with 2-[18F]-fluoro-2-deoxy-D-glucose-positron emission tomography and computed tomography registration. J Comput Assist Tomogr 2003;27:479-84.
125. Cerfolio RJ, Ojha B, Bryant AS, et al. The accuracy of integrated PET-CT compared with dedicated PET alone for the staging of patients with nonsmall cell lung cancer. Ann Thorac Surg 2004;78:1017-23; discussion 1017-23.
126. Stiles BM, Servais EL, Lee PC, et al. Point: Clinical stage IA non-small cell lung cancer determined by computed tomography and positron emission tomography is frequently not pathologic IA non-small cell lung cancer: the problem of understaging. J Thorac Cardiovasc Surg 2009;137:13-9.
127. Cerfolio RJ. Counterpoint: Despite staging inaccuracies, patients with non-small cell lung cancer are best served by having integrated positron emission tomography/computed tomography before therapy. J Thorac Cardiovasc Surg 2009;137:20-2.
128. Wolthaus JW, Sonke JJ, van Herk M, et al. Comparison of different strategies to use four-dimensional computed tomography in treatment planning for lung cancer patients. Int J Radiat Oncol Biol Phys 2008;70:1229-38.
129. Latifi K, Oliver J, Baker R, et al. Study of 201 non-small cell lung cancer patients given stereotactic ablative radiation therapy shows local control dependence on dose calculation algorithm. Int J Radiat Oncol Biol Phys 2014;88:1108-13.
130. Huang K, Dahele M, Senan S, et al. Radiographic changes after lung stereotactic ablative radiotherapy (SABR)--can we distinguish recurrence from fibrosis? A systematic review of the literature. Radiother Oncol 2012;102:335-42.

Cite this article as: Roesch J, Andratschke N, Guckenberger M. SBRT in operable early stage lung cancer patients. Transl Lung Cancer Res 2014;3(4):212-224. doi: 10.3978/j.issn.2218-6751.2014.08.06

Current Evidence

Alternatives to surgery in early stage disease—stereotactic body radiotherapy

Meredith Elana Giuliani[1,2], **Andrea Bezjak**[1,2]

[1]Radiation Medicine Program, Princess Margaret Hospital, Toronto, Ontario, Canada; [2]Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada

Correspondence to: Dr Andrea Bezjak, Professor, Radiation Oncologist. Department of Radiation Oncology, University of Toronto, Princess Margaret Cancer Centre, 610 University Ave, Toronto, ON, M5G2M9, Canada. Email: Andrea.Bezjak@rmp.uhn.on.ca.

Abstract: The management of early stage non-small cell lung carcinoma (NSCLC) has been revolutionized by the introduction of stereotactic body radiotherapy (SBRT). SBRT is now the standard of care for medically inoperable patients with early stage NSCLC. However, the role of SBRT in medically operable patients remains controversial. This article will review the indications, the technical considerations, image guidance principles, potential toxicities and special circumstances in lung SBRT.

Keywords: Local control; non-small cell lung carcinoma; stereotactic body radiotherapy; stereotactic ablative radiotherapy; toxicity

Submitted Oct 05, 2013. Accepted for publication Oct 13, 2013.
doi: 10.3978/j.issn.2218-6751.2013.10.10
View this article at: http://www.tlcr.org/article/view/1606/2330

Introduction

The strictest definition of early stage non-small cell lung carcinoma (NSCLC) refers to patients with T1-2aN0 tumors (1). This chapter will focus on the management of these early stage NSCLC with radiotherapy, and specifically with high dose high precision stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR).

Currently the standard or care for early stage NSCLC is lobectomy in patients who are suitable candidates (2). However, many patients are not suitable for lobectomy due to medical co-morbidities, pulmonary function or in some circumstances patient preference. The surgical alternatives to lobectomy, in the form of sublobar resections, are being explored in such patients. Radiotherapy is an option for patients who are not able to undergo surgical resection. We do not recommend observation in this patient population, unless the patient is estimated to have an extremely limited life expectancy from comorbidities, as the median survival in patients with untreated stage I NSCLC is 14 months and the majority die of lung cancer (3). In a population based study, the introduction of SBRT lead to a reduction in the proportion of patients receiving no treatment for their early stage lung cancer, and also significantly improved the survival of patients with early stage lung cancer at the population level (4).

Prior to the widespread use of SBRT, radiotherapy involved 6 to 7 weeks of treatment with standard dose fractionation of 2 Gy per fraction daily; typical doses were 60 Gy in 30 fractions or more, to the primary tumor and surrounding lung ("involved field") and occasionally to the lymph node regions deemed at risk of harboring microscopic disease. These regimens have the advantage of conventional dose per fraction, with potentially less late normal tissue injury (although these doses are well above radiation tolerance of lung, and some amount of lung fibrosis is to be expected), but a lower biological dose. With lower biological doses there is an expected lower rate of long-term local control (5). Clinical outcomes were generally poor with local failures occurring in approximately 40% of patients (6). The focus of therapy turned to dose escalation in the hope of improving clinical outcomes, specifically local control in this patient population.

Dose escalation strategies occurred in the form of hypofractionated regimens. Common regimens used at

our institution which have acceptable efficacy, 20% local failure at 5 years, and are well tolerated are 60 Gy in 20 fractions or 50 Gy in 20 fractions (7). A Canadian national phase II study in peripheral tumors using 60 Gy in 15 fractions reported 2-year actuarial local control of 88% and 2-year overall survival of 69%. The most frequent toxicities were fatigue, cough and dyspnea. Radiation pneumonitis occurred in 10% of patients (8).

Stereotactic body radiotherapy (SBRT)

Lung SBRT or SABR involves using few high dose fractions to treat small target volume (9) guided by a set of coordinates (thus the term "stereotactic"). These coordinates are set in relationship to the precise location of the tumor, rather than a set of external marks (tattoos) or anatomical landmarks (such as bony structures), which is typical for conventional RT. The principles of body SBRT are an adaptation of the principles and experience gained from stereotactic brain RT, a well-established high-precision RT technique that uses a set of coordinates on a stereotactic frame afixed to the patient's head, to direct multiple beams to a well-defined intracranial target. This allows the delivery of high doses of RT to the target while minimizing the exposure of normal tissue. In the case of lung cancer, the coordinates are set in relationship to the tumor itself, which can be visualized either directly with volumetric imaging such as cone-beam CT which is part of a linear accelerator, or localized through use of implanted fiducial markers, akin to what has been used with gold seed implants for prostate radiotherapy.

In addition to the use of tumor localization in the three dimensions, other important principles of stereotactic RT that need to be applied to lung SBRT are the precise outline (contouring) of a well-defined target (tumor), identification of a relatively tight (small) planning target volume (PTV) by minimizing target motion and set-up variation, conformal RT planning, using multiple small beams coming from various directions and planes, daily set-up verification prior to each treatment and the use of high RT doses that can ensure high rates of tumor cell kill.

Several single center and multicenter prospective studies, as well as numerous retrospective reports have established the safety and efficacy of lung SBRT for early stage lung cancer. There are many dose and fractionation schedules used. Local control in the order of 85-90% has been reported with most dose-fractionation schedules that provide a biologic effective dose (BED) of 100 Gy or more (10). Those schedules include 48 Gy in 4 fractions (of 12 Gy each), 55 Gy in 5 fractions (of 11 Gy each), 60 Gy in 8 fractions (of 7.5 Gy each), and 54-60 Gy in 3 fractions (of 18-20 Gy per fraction). The choice of schedule and dose depends on tumor size, location and institutional experience/preference.

In the context of lung SBRT tumors are generally <5 cm. SBRT may be considered for T1-2N0M0 and select <5 cm T3N0M0 chest wall NSCLC (11). It is our practice to deliver 54 Gy in 3 fractions for larger peripheral tumors, away from organs at risk (OAR), 48 Gy in 4 fractions for peripheral tumors <3 cm in diameter and 60 Gy in 8 fractions for centrally located tumors (i.e., tumors within a 2 cm radius of the airway or great vessels). The optimal dose for centrally located tumors is controversial and is awaiting analysis and reporting of the phase I/II RTOG study 0813 (12). In the phase II multicenter RTOG 0236 study, SBRT for early stage NSCLC in medically inoperable patients, with 60 Gy/3 fractions (equivalent to 54 Gy/3 fractions when corrected for lung tissue heterogeneity) was associated with a 3-year 98% tumor control, 91% local control and 56% overall survival (OS) (13).

Accurate mediastinal staging in potential candidates from SBRT is essential. Traditionally, patients who receive surgical resection for early stage NSCLC would have invasive mediastinal staging, either preoperative or intraoperative. In surgical patients staged preoperatively with PET/CT as N0, the occult node positivity rate at the time of surgery is 18%. Patients with tumors >3 cm or high SUVmax are at higher risk of occult nodal metastasis (14). Thus, before proceeding with SBRT, patients should at a minimum have PET staging and biopsy of any enlarged or suspicious nodes, and there may be merit in EBUS staging of other SBRT candidates who are at a high risk occult nodal disease. However, despite the absence of rigorous staging, the incidence of nodal relapse following SBRT is low, 5-10% in most series; low dose irradiation to first eschalon nodal regions has been postulated as one possible cause and immune effect of SBRT to the primary lesion in causing a presentation of antigens and resultant immune response that may control other areas of micro-metastatic disease (15), have been postulated as explanations, both have some evidence supporting them.

Technological considerations

As described above, SBRT is a technically rigorous treatment which requires precise tumor localization and treatment delivery to minimize the potential for significant toxicity

Figure 1 Abdominal compression plate as used in lung SBRT.

Figure 2 Stereotactic body frame.

to normal structures or organs at risk (OARs) (16). To accomplish this one must consider immobilization strategies, respiratory motion control, accurate target delineation, advanced planning algorithms and image guidance (17). We will briefly review the major technological considerations for the planning and delivery of SBRT focusing on motion management and image guidance.

Motion management

All intrathoracic tumors are affected by respiratory movement. Respiratory motion management is an essential component for the successful delivery of lung SBRT (17). There are two major strategies to manage motion in lung SBRT. The first involves reducing respiratory excursion, typically either through abdominal compression or active breathing control (ABC) (*Figure 1*). In some institutions tumor motion is restricted in all patients, in other institutions it is restricted in select circumstances and some institutions employ no motion restriction. When motion restriction is used selectively, a threshold is selected, commonly 1 cm (17). In our institution, using that threshold, less than 25% of patients, require abdominal compression to manage respiratory motion (17).

The second method of motion management involves using real-time tumor tracking to intermittently delivery radiotherapy when the target is in the treatment position, this is referred to as "gating". Regardless of the technique used to manage tumor motion, accurate analysis and interpretation of the motion observed on the 4D planning CT scan and accurate localization of the tumor at the time of SBRT delivery is essential to ensure ablation of the tumor and sparing of critical structures.

Target localization

The Stereotactic Body Frame (SBF) was the immobilization strategy used in the earliest reports of extracranial SBRT (18,19) (*Figure 2*). Those early reports emphasized the importance of patient immobilization and accurate repositioning for multi-fraction treatments (9). Clinical outcomes with frame-based SBRT strategies were acceptable (20) however this technique requires a significant amount of treatment unit time and special equipment had to be purchased with staff trained to use it. Now, image guided strategies have been widely implemented to replace the SBF. Continued improvements in the delivery of frameless SBRT offer potential improvements in clinical outcome. Patients with poorer performance status drift more in position during SBRT (21). A change in the delivery of SBRT from multiple static beams to more contemporary volumetric modulated arc therapy (VMAT) affords a faster treatment time which may improve position accuracy by affording less time for patients to drift out of position.

Several techniques can be used to confirm the tumor

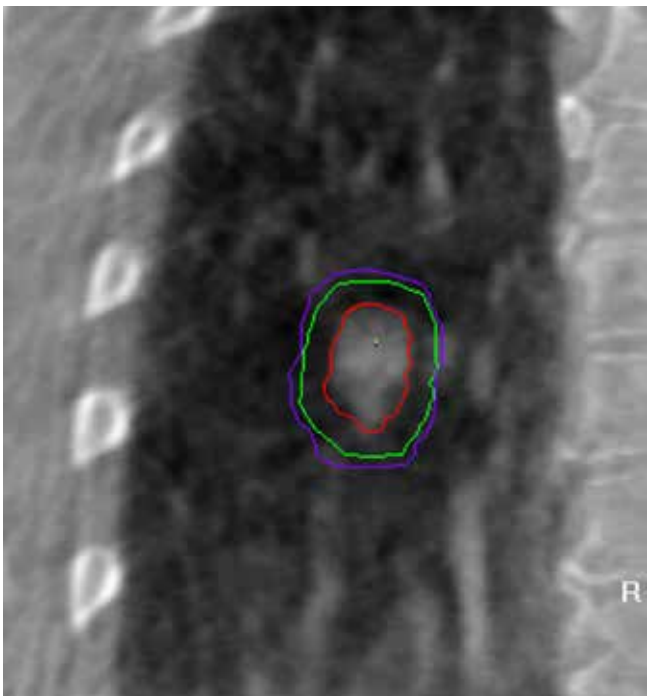


Figure 3 Cone beam CT images taken prior to SBRT. Red line represents the internal target volume (ITV), the green line represents the planning target volume (PTV) and the purple line represents the 95% isodose line from the radiotherapy plan included as a reference.

location just before or during radiotherapy. These techniques include: CT-on-rails (22), real-time tumor gating (23), TomoTherapy (24), CBCT (25), and Cyberknife (real-time tumor tracking using a robotic system) (26). The conceptual principles are as discussed above, the practical details differ depending on the system. *Figure 3* demonstrates how cone beam images on the treatment unit can be used to position the patient more accurately and guide the radiation beams directly onto the tumor target.

Patient selection for SBRT

SBRT has most widely been adopted for tumors located in the periphery of the lung. In a prospective phase II study conducted by the RTOG the 3-year primary tumor control for stage I/II NSCLC treated with 18 Gy ×3 fractions was 97.6% with only 1 local failure in 55 patients. The lobar control rate at 3 years was 90.6% and the 3-year disease free survival was 48.3% (27). Overall the regimen was well tolerated with 7 patients with grade 3 toxicity and 2 patients with grade 4 toxicity. There were no grade 5 toxicities (27).

SBRT is most commonly used for patients with tumors <5 cm however some centers do deliver SBRT to larger tumors. In our experience, larger tumors still had comparable rates of local control but had higher rates of regional and distant failures, and somewhat higher rates of grade 2 pneumonitis (28).

SBRT toxicity

The rate of adverse events following SBRT is low, however in some circumstances has been severe or fatal (16). The most common side effect in the acute phase is fatigue which is typically mild (grade 1) and seen in approximately 50% of patients (11). Radiation pneumonitis can occur in the 6 weeks to 9 months following SBRT. More uncommon but worrisome due to the catastrophic nature of the outcomes are toxicities related to the central mediastinal structures such as the major vessels (aorta, vena cava etc.) and the proximal airways. Rarely, grade 4 and 5 toxicities such as massive hemoptysis have been reported following SBRT, almost exclusively in the cases of central tumors (29).

Rib fractures and chest wall pain are two side-effects that are almost never reported after conventional fractionated radiotherapy, but have become widely reported and recognized to be associated with SBRT (30). Rib fractures are often asymptomatic and should not be mistaken for bone metastases (*Figure 4*). In a dosimetric and clinical multivariate analysis age, female gender and D0.5 were significantly associated with rib fractures following SBRT (31).

Radiation pneumonitis, a limiting toxicity with conventional RT for lung cancer, and associated with the volume of lung being treated (32) is less commonly reported in patients treated with SBRT, likely due to much smaller volumes treated, even though most patients treated with SBRT have limited lung function. One series reported that grade ≥2 pneumonitis occurred in 11% of patients (29). The risk of radiation pneumonitis is associated with increasing mean lung dose (29).

Similarly, there is minimal reduction of pulmonary function after SBRTand this treatment is suitable even for patients with severe COPD who are oxygen-dependent. At our institution we do not have a minimum cut-off for FEV1 or DLCO. All patients are considered on an individual basis for suitability for SBRT. The only group of patients who are at a higher risk of pulmonary toxicity are patients with idiopathic pulmonary fibrosis.

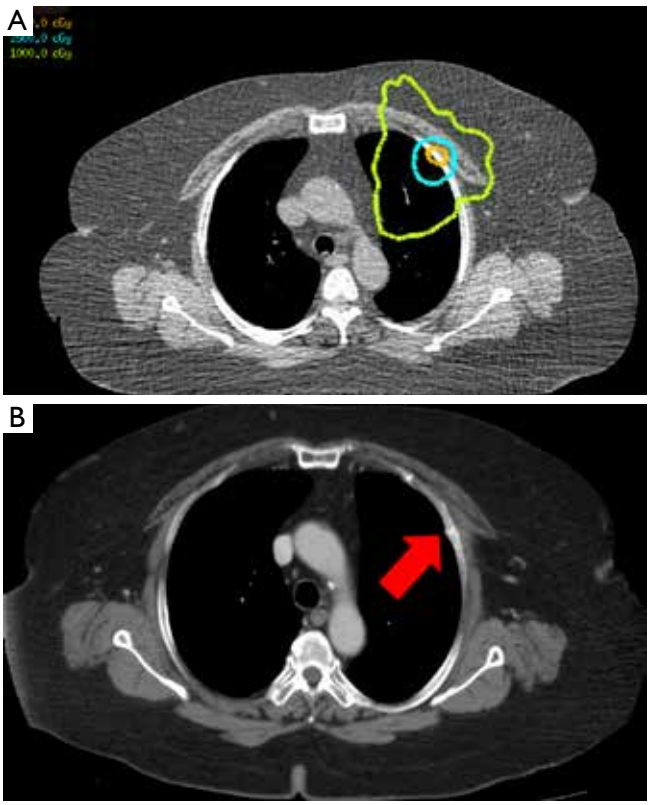


Figure 4 Rib fracture and dosimetric overlay from a Lung SBRT Plan. (A) The orange line represents the 4,320 cGY isodose line, the blue line represents with 2,500 cGy isodose line and the green line represents the 1,000 cGy isodose line; (B) the red arrow indicates the rib fracture.

Radiographic changes following SBRT

The majority of patients have significant radiographic changes in their lung parenchyma following SBRT. These changes gradually develop in the 6 to 12 months following SBRT. Although the majority of patients have developed some degree of radiographic changes 12 months following SBRT the nature of these changes continue to evolve over time. There is no consensus as to how best to categorize these changes however work by Dahele *et al.* proposes a 4 category classification system for late post-SBRT radiographic changes. These categories are: modified conventional pattern, Mass-like fibrosis, Scar-like fibrosis and No evidence of increased density.

These radiographic changes make assessment of local control of the treated tumor following SBRT challenging. Several authors have proposed CT characteristic which may be associated with tumor recurrence as opposed to benign radiographic changes however these have not been independently validated.

The ability to accurately identify patients with residual or recurrent tumors is increasingly important as SBRT is used in operable patients where surgical salvage for a local recurrence may be an option. Further work on other imaging modalities such as MRI, perfusion CT or FLT-PET may be of clinical benefit.

Central tumors

Centrally located tumors require careful consideration when treated with SBRT. Two criteria are currently applied to identify tumors as central: the RTOG 0236 study defined them as tumors that are "within or touching the zone of the proximal bronchial tree defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi)" (33). The RTOG 0813 trial in addition also defined as central those "tumors that are immediately adjacent to mediastinal or pericardial pleura (PTV touching the pleura)" (12). Some institutions consider central tumors to also be any tumor within 2 cm of any mediastinal structure (34) although with careful planning, avoidance of mediastinal structures should be possible in most of the latter group.

Timmerman *et al.* reported an excess of respiratory events in patients who received 60 Gy in 3 fractions to centrally located tumors (16). Patients with central tumors had a 2-year freedom from severe toxicity of 54%, significantly lower than patients with peripheral tumors (84%) (16). Thus lead to the introduction of modified fractionations schedules for central tumors. There is significant heterogeneity in institutional practices in that regard, and most try to achieve a BED of 100 or greater. In a patterns-of-practice survey the majority of clinicians preferred a slightly more protracted fractionation schedule (≥4 fractions) for centrally located tumors (35). It is our institutional practice to deliver 60 Gy in 8 fractions; this is supported by data from the NKI group (11,34). Other institutions have reported 50 Gy in 4 fractions (36,37), 48 Gy in 4 fractions (38), 48 Gy in 6 fractions (39), or 60 Gy in 5 fractions (39).

The RTOG phase I/II trial in patients with centrally located tumors has reached the highest planned dose level of 60 Gy in 5 fractions (12) although analysis needs to await the full one year follow-up to determine whether this is

indeed the maximum tolerated dose. The hope is that this study will establish a safe and efficacious dose fractionation for central tumors and will also provide novel data on the radiation tolerance of mediastinal structures.

Medically operable patients

SBRT is now the standard of care in the majority of centers for patients who cannot have surgery for early stage NSCLC. The role of SBRT in patients who are surgical candidates remains controversial. The RTOG has completed accrual to a phase II study exploring the 2-year local control rate in medically operable patients treated with SBRT (40). A review by Onishi *et al.* of SBRT in medically operable patients who refused surgery reported a promising 5-year local control rate of 92% for T1 tumors and 73% for T2 tumors. The 5 year overall survival was 72% for T1 and 62% for T2 tumors (41). However, to conclusively assess the efficacy and safety of SBRT in operable patients compared to surgical resection, randomized data is needed. It is challenging to randomize patients to such different treatment modalities however, several phase III trials have been opened but all had to close due to poor accrual (42). Case-control studies that have included propensity matching (43) have demonstrated that SBRT results are at least equivalent and quite possibly superior to surgery, especially if compared to wedge resection. This is indeed intriguing and provides a solid foundation to offer SBRT even to surgical candidates.

Conclusions

SBRT is a safe and effective treatment for patients with early stage NSCLC who cannot undergo surgical resection. Further studies are needed to determine the safe standard of practice for centrally located tumors and to determine the role of SBRT in medically operable patients.

Acknowledgements

Disclosure: Drs Bezjak and Giuliani have received travel funding from Elekta Inc and Dr Bezjak has received research support from Elekta Inc in the past.

References

1. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual. Chicago, IL, American Joint Committee on Cancer, 2010
2. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
3. Raz DJ, Zell JA, Ou SH, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. Chest 2007;132:193-9.
4. Wisnivesky JP, Bonomi M, Henschke C, et al. Radiation therapy for the treatment of unresected stage I-II non-small cell lung cancer. Chest 2005;128:1461-7.
5. Fang LC, Komaki R, Allen P, et al. Comparison of outcomes for patients with medically inoperable Stage I non-small-cell lung cancer treated with two-dimensional vs. three-dimensional radiotherapy. Int J Radiat Oncol Biol Phys 2006;66:108-16.
6. Qiao X, Tullgren O, Lax I, et al. The role of radiotherapy in treatment of stage I non-small cell lung cancer. Lung Cancer 2003;41:1-11.
7. Yung T, Giuliani ME, Le LW, et al. Outcomes of accelerated hypofractionated radiotherapy in stage i non-small-cell lung cancer. Curr Oncol 2012;19:e264-9.
8. Cheung P, Faria S, Ahmed S, et al. A Phase II Study of Accelerated Hypofractionated 3-Dimensional COnfirmal Radiotherapy for Inoperable T1-3N0M0 Non-Small Cell Lung Cancer; NCIC CTG BR.25. Radiotherapy & Oncology 2012;104:S67.
9. Wulf J, Hädinger U, Oppitz U, et al. Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame Radiother Oncol 2000;57:225-36.
10. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004;101:1623-31.
11. Taremi M, Hope A, Dahele M, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. Int J Radiat Oncol Biol Phys 2012;82:967-73.
12. Bezjak A. RTOG 0813: Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients. Available online: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0813
13. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer.

JAMA 2010;303:1070-6.
14. Li L, Ren S, Zhang Y, et al. Risk factors for predicting the occult nodal metastasis in T1-2N0M0 NSCLC patients staged by PET/CT: potential value in the clinic. Lung Cancer 2013;81:213-7.
15. Lee Y, Auh SL, Wang Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood 2009;114:589-95.
16. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
17. Dahele M, Pearson S, Purdie T, et al. Practical considerations arising from the implementation of lung stereotactic body radiation therapy (SBRT) at a comprehensive cancer center. J Thorac Oncol 2008;3:1332-41.
18. Lax I, Blomgren H, Näslund I, et al. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. Acta Oncol 1994;33:677-83.
19. Blomgren H, Lax I, Näslund I, et al. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 1995;34:861-70.
20. Yoon SM, Choi EK, Lee SW, et al. Clinical results of stereotactic body frame based fractionated radiation therapy for primary or metastatic thoracic tumors. Acta Oncol 2006;45:1108-14.
21. Li W, Purdie TG, Taremi M, et al. Effect of immobilization and performance status on intrafraction motion for stereotactic lung radiotherapy: analysis of 133 patients. Int J Radiat Oncol Biol Phys 2011;81:1568-75.
22. Uematsu M, Shioda A, Suda A, et al. Intrafractional tumor position stability during computed tomography (CT)-guided frameless stereotactic radiation therapy for lung or liver cancers with a fusion of CT and linear accelerator (FOCAL) unit. Int J Radiat Oncol Biol Phys 2000;48:443-8.
23. Shirato H, Shimizu S, Shimizu T, et al. Real-time tumour-tracking radiotherapy. Lancet 1999;353:1331-2.
24. Mackie TR, Kapatoes J, Ruchala K, et al. Image guidance for precise conformal radiotherapy. Int J Radiat Oncol Biol Phys 2003;56:89-105.
25. Jaffray DA, Drake DG, Moreau M, et al. A radiographic and tomographic imaging system integrated into a medical linear accelerator for localization of bone and soft-tissue targets. Int J Radiat Oncol Biol Phys 1999;45:773-89.
26. Gibbs IC. Frameless image-guided intracranial and extracranial radiosurgery using the Cyberknife robotic system. Cancer Radiother 2006;10:283-7.
27. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
28. Allibhai Z, Hope A, Sun A, et al. The impact of tumour size on outcomes following stereotactic body radiotherapy for medically inoperable early-stage non-small cell lung cancer. International Journal of Radiation Oncology, Biology & Physics 2013. (In Press).
29. Borst GR, Ishikawa M, Nijkamp J, et al. Radiation pneumonitis in patients treated for malignant pulmonary lesions with hypofractionated radiation therapy. Radiother Oncol 2009;91:307-13.
30. Voroney JP, Hope A, Dahele MR, et al. Chest wall pain and rib fracture after stereotactic radiotherapy for peripheral non-small cell lung cancer. J Thorac Oncol 2009;4:1035-7.
31. Taremi M, Hope A, Lindsay P, et al. Predictors of radiotherapy induced bone injury (RIBI) after stereotactic lung radiotherapy. Radiat Oncol 2012;7:159.
32. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1999;45:323-9.
33. RTOG 0236. A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer, Available online: http://intranet.rmp.uhn.on.ca/AssetFactory.aspx?did=9471. January 2013, 2004.
34. Haasbeek CJ, Lagerwaard FJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. J Thorac Oncol 2011;6:2036-43.
35. Daly ME, Perks JR, Chen AM. Patterns-of-care for thoracic stereotactic body radiotherapy among practicing radiation oncologists in the United States. J Thorac Oncol 2013;8:202-7.
36. Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;72:967-71.
37. Rowe BP, Boffa DJ, Wilson LD, et al. Stereotactic body radiotherapy for central lung tumors. J Thorac Oncol 2012;7:1394-9.
38. Stauder MC, Macdonald OK, Olivier KR, et al. Early pulmonary toxicity following lung stereotactic body

radiation therapy delivered in consecutive daily fractions. Radiother Oncol 2011;99:166-71.
39. Nuyttens JJ, van der Voort van Zyp NC, Praag J, et al. Outcome of four-dimensional stereotactic radiotherapy for centrally located lung tumors. Radiother Oncol 2012;102:383-7.
40. Timmerman RD. RTOG 0618: A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer, Available online: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0618, 2010.
41. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352-8.
42. Hurkmans CW, Cuijpers JP, Lagerwaard FJ, et al. Recommendations for implementing stereotactic radiotherapy in peripheral stage IA non-small cell lung cancer: report from the Quality Assurance Working Party of the randomised phase III ROSEL study. Radiat Oncol 2009;4:1.
43. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol 2010;28:928-35.

Cite this article as: Giuliani ME, Bezjak A. Alternatives to surgery in early stage disease—stereotactic body radiotherapy. Transl Lung Cancer Res 2013;2(5):332-339. doi: 10.3978/j.issn.2218-6751.2013.10.10

Additional data in the debate on stage I non-small cell lung cancer: surgery versus stereotactic ablative radiotherapy

Charles B. Simone II, Jay F. Dorsey

Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, USA

Correspondence to: Charles B. Simone II, MD. Perelman Center for Advanced Medicine, Perelman School of Medicine, University of Pennsylvania, TRC2W, 3400 Civic Center Boulevard, Philadelphia, PA 19104-5156, USA. Email: charles.simone@uphs.upenn.edu; Jay F. Dorsey, MD, PhD. Smilow Center for Translational Research, Perelman School of Medicine, University of Pennsylvania, Building 421, Room 8-135, 3400 Civic Center Boulevard, Philadelphia, PA 19104-5156, USA. Email: jayd@uphs.upenn.edu.

Abstract: Lobectomy has been the standard of care for patients with early stage non-small cell lung cancer (NSCLC), resulting in nearly universal local control and excellent overall survival. However, up to one-quarter of early stage patients are unable to undergo or refuse definitive resection. With the increasing adoption of stereotactic ablative radiotherapy (SABR) over conventionally fractionated radiotherapy among medical inoperable patients, tumor control and overall survival rates in this population have significantly improved. Trials demonstrating excellent outcomes among both medically inoperable and medical operable patients with stage I NSCLC have spurred interest in comparisons between surgery and SABR. The recent publication of the randomized STARS and ROSEL trials demonstrated fewer toxicities and an improvement in overall survival among patients treated with SABR compared with surgery. Based on these trials and retrospective comparisons between the modalities, definitive SABR now more firmly appears to be a viable first-line option for treating patients with operable stage I NSCLC.

Keywords: Lobectomy; lung cancer; randomized; stereotactic ablative radiotherapy (SABR); stereotactic body radiation therapy (SBRT)

Submitted Jul 15, 2015. Accepted for publication Jul 23, 2015.
doi: 10.3978/j.issn.2305-5839.2015.07.26
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.07.26

Introduction

More than 1.8 million people are estimated to be diagnosed worldwide with lung and bronchus cancers annually. Despite improvements in therapies and increased efforts towards smoking cessation, lung cancer continues to be the greatest cause of mortality from cancer, with an estimated 1.6 million deaths expected globally each year (1). Non-small cell lung cancer (NSCLC) accounts for approximately 87% of new lung cancer diagnoses, and approximately 15% of patients with NSCLC have localized diseased confined to their primary tumor site at the time of diagnosis (2,3). Additionally, the incidence of early stage NSCLC is expected to continue to rise with the increasing life expectancy in elderly patients, advances in medical imaging, implementation of low-dose computed tomography lung cancer screening programs based on the findings of the National Lung Screening Trial (4,5), and increasing investigation into circulating tumor products and other potential methods of early NSCLC detection (6).

Surgery-based standard of care

Surgery has been long established to be the preferred treatment option for patients with early stage NSCLC, particularly those with tumors ≤5 cm in size without local invasion (7,8). Based on available literature, the American College of Chest Physicians Evidence-based Clinical Practice Guidelines in 2007 determined that "surgical resection remains the treatment of choice for stage I and II NSCLC" (8). Lobectomy or greater anatomical resection has consistently been reported to achieve local control rates of >90% for stage I NSCLC and generally is the preferred surgical approach over sublobar resections with wedge resection or segmentectomy (8,9). In patients able

to tolerate operative interventions but thought not to be able to undergo a lobar resection, those clinical practice guidelines recommend sublobar resection over nonsurgical intervention such as radiation therapy (8) or other ablative techniques (10).

Although surgery is the most oncologic way to treat early stage NSCLC, resection does have several limitations. First, at least 15-20% of patients diagnosed with stage I NSCLC are unable to undergo or refuse definitive surgical resection (11,12). Second, complication rates following surgery are not trivial, especially among older patients and those with higher comorbidity index scores. In fact, a recent National Cancer Data Base study assessing 124,418 major lung resections from 2007 to 2011 found a 30-day mortality rate of 2.8% and 90-day mortality rate of 5.4% (13). Furthermore, although lobectomy is considered the standard-of-care surgical procedure for stage I NSCLC, 5-15% of patients require a bilobectomy and another 4-15% require a pneumonectomy (14), which are known to increase the risk of perioperative mortality compared with lobectomy (13).

Advent of stereotactic body radiotherapy

For patients who are medically inoperable, radiotherapy delivered with conventional fractionation, typically in 1.8-2.0 Gy daily fractions, has been employed as standard therapy but was generally reserved for patients of borderline resectability, who were medically-inoperable with cardiovascular or chronic pulmonary diseases, or who refused surgery (8,15,16). Therefore, patients with stage I NSCLC treated with definitive radiotherapy have generally been older with higher medical comorbidity scores and higher rates of intercurrent non-cancer mortality than patients undergoing surgery. As a result, the reported 5-year survival and local control rates after conventionally fractionated radiotherapy of 17-55% and 40-70%, respectively, have been far inferior to the rates of 50-80% and 80-95% with anatomical surgical resection (17).

Dose escalation and altered fractionation regimens were investigated to attempt to improve the poor local control rates seen after conventionally fractionated radiotherapy. Early reports using hypofractionation (fraction sizes greater than standard 1.8-2.0 Gy fractions) to smaller radiotherapy fields without prophylactic irradiation to nodal regions at risk of developing metastasis demonstrated improved local control and overall survival compared with conventionally fractionated radiotherapy (18,19). Based on these findings and the successful applications of high dose stereotactic radiosurgery for primary and metastatic brain tumors, high dose stereotactic treatments were investigated. Early clinical applications of this approach to treat early stage NSCLC, termed stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR), began in the late 1990's.

SABR involves the administration of ulta-high dose, ablative fractions of radiation to a target, which allows for maximizing cell-killing effect of tumor thought to be from the delivery of higher biological equivalent doses of radiotherapy than can be achieved with conventional fractionation. In contrast to conventional irradiation, which is delivered daily for six to eight weeks, SABR is typically administered in one to give fractions in doses of 6-34 Gy per fraction. Through a rapid dose falloff gradient that compasses the tumor, SABR can also minimize irradiation received by surrounding normal organs (17,20,21). SABR requires accurate delineation of the tumor and accurate and reproducible localization of the target lesion relative to a known three dimensional reference system, generally with image-guided radiotherapy used to verify patient positioning and tumor localization before to each fraction (22,23).

Across prospective and retrospective studies, SABR results in local control rates of 80-100% and overall survival rates of 40-80% at 3 years in medically inoperable patients (17). An early phase II study of 70 patients treated with SBRT to 60-66 Gy in 3 fractions found the local control to be 95% and overall survival to be 55% at 2-years (24). The first multi-centered cooperative group phase II trial [Radiation Therapy Oncology Group (RTOG) 0236] found a 3-year primary tumor local control rate of 97.6%, local-regional control rate of 87.2%, and overall survival rate of 55.8% among 55 patients with stage I NSCLC treated in three fractions with SBRT to 54 Gy (25).

These excellent outcomes among medically inoperable patients have spurred interest in investigating SABR in potentially operable patients with stage I NSCLC (26,27). In a study of 87 patients with stage I NSCLC who were medically operable but refused surgery, treatment with SABR to 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, with overall survival rates of 72% for stage IA and 62% for IB, which are comparable to outcomes reported in surgical series (28).

Mature data from completed phase II trials of SBRT in medically-operable patients are pending. In an interim analysis of Japan Clinical Oncology Group (JCOG 0403), 65 patients with medically operable cT1N0M0 NSCLC

were treated with SABR in 4 fractions to 48 Gy. At a median follow-up of 45.4 months, the overall survival was 76.0%, progression-free survival was 54.5%, and local-progression free survival was 68.5% at 3 years. Toxicity was limited to grade 3 chest pain (1.5%), dyspnea (3.1%), hypoxia (1.5%), and pneumonitis (3.1%), without any grade 4 or 5 toxicities observed (29). In an interim analysis of RTOG 0618, 26 evaluable patients with cT1-T2N0M0 NSCLC were treated in three fractions to 54 Gy. At a median follow-up of 25 months, the overall survival was 84.4%, progression-free survival was 65.4%, primary tumor failure was 7.7%, regional failure was 11.7%, and distant failure was 15.4% at 2 years. Sixteen percent had grade 3 toxicities, while no grade 4-5 toxicities were observed (30).

Across studies, SABR has generally been shown to be well tolerated. Acute SABR complications, including fatigue, skin erythema, mild hematologic suppression and cough, are typically mild and transient and occur in 5-40% of patients (26). Subacute and late toxicities are less common but potentially more severe and can include radiation pneumonitis, chronic dyspnea, hemoptysis, chest wall pain, rib fracture, bronchial stenosis or necrosis, esophageal injury, and brachial plexopathy (17). High grade morbidity and even mortality has been reported with SABR delivered to centrally located tumors within 2 cm of the proximal bronchial tree (26), although treatment of central tumors with SABR can be effective and appears safer when delivered in regimens of greater than three fractions (31).

Surgery versus SABR

Given the efficacy of SABR reported in both medically inoperable and operable patients with stage I NSCLC, there has been much interest in comparing SABR with surgical resection. However, direct comparisons from retrospective and population-based studies have been faced with challenges. Patients who have undergone SABR have generally been older and had higher comorbidity index scores than those undergoing surgery, potentially biasing survival comparisons in favor of surgery. Additionally, differences exist in how some studies have defined local failure. Surgical series have define local failure variably as recurrence within the same lobe, another lobe of the ipsilateral lung, or regional lymph nodes, whereas many SABR series have defined local failure as progression at the site of the primary tumor or within the high dose treatment region, potentially biasing local control comparisons in favor of SABR.

Furthermore, patients treated with SABR have generally received less extensive or less invasive lymph nodal staging compared with patients undergoing definitive surgical therapy who generally undergo a lymph node dissection at the time of primary tumor resection. Up to one-third of patients treated with SABR for presumed stage I NSCLC might actually have more advanced disease and nodal metastasis (32), potentially biasing survival comparisons in favor of surgery. This is not a trivial point given that data from over 18,000 patients analyzed as part of the IASLC Lung Cancer Staging Project demonstrated a dramatic reduction in overall survival based on clinical stage when compared to surgical stage (33).

Despite these and other limitations, some existing comparisons between the modalities are noteworthy. In an early retrospective comparison of 124 patients with stage I NSCLC who were ineligible for lobectomy treated with SABR (n=58) or wedge resection (n=69) at William Beaumont Hospital, SBRT patients were found to be older and have higher comorbidity scores. However, SBRT was associated fewer local recurrences (5% *vs.* 24%, P=0.05) and locoregional recurrences (5% *vs.* 29%, P=0.03). There was no difference in cause-specific survival (93% *vs.* 94%, P=0.53), but SBRT patients had an inferior overall survival (72% *vs.* 87%, P=0.01) most consistent with pre-treatment differences between patients receiving each modality (34).

In another early retrospective comparison of 464 patients who underwent surgery and 76 who underwent SABR for clinical stage I NSCLC at Washington University, local control at 3 years was improved with surgery for stage IA patients (96% *vs.* 89%, P=0.04) but no different for stage IB patients (P=0.89). Although no difference in disease-specific survival was seen, surgery was associated with improved overall survival, potentially also in part due to patients receiving surgery being younger, having lower comorbiditity scores, and having better pulmonary function (all P<0.001). In a matched analysis of higher risk surgery patients (n=57) to SABR patients, no difference was seen in local recurrence, disease-free survival, or overall survival at 3 years (all P>0.05) (35). In their updated T-stage matched analysis of patients treated with lobar resection (n=260) or SBRT (n=78), there was no significant difference in patterns of failure or cause-specific survival, whereas overall survival favored surgery (36).

Investigators from the Netherlands have published a series of studies comparing surgery and SABR. In a propensity score-matched analysis based on stage, age, gender, comorbidity score, lung function, and performance

status, locoregional control rates were higher in patients receiving SABR (n=64) than those receiving VATS (n=64) (86.9% *vs.* 82.6%, P=0.04), whereas there was no difference in distant recurrence rate or overall survival (37). In an updated propensity score-matched analysis (n=73 for each modality), survival was similar (P=0.089) at 12 months (95% *vs.* 94%) and 60 months (80% *vs.* 53%) for patients undergoing surgery and SABR, with a trend towards improved survival with surgery at longer follow-up identified (38). In a recent publication of stage I NSCLC patients treated with surgery (n=143) or SABR (n=197), survival was similar across modalities when controlling for prognostic covariables (P=0.73). When examining recurrences, local and distant control were similar but locoregional recurrences occurred more following SABR (P=0.028), suggesting a need to improve staging in SABR-treated patients (39).

Surveillance, Epidemiology, and End Results (SEER) studies and systematic reviews have also compared surgery and SABR. Among 10,923 patients aged ≥66 years with stage I NSCLC treated from 2001-2007, the majority (59%) were treated with lobectomy, whereas only 1.1% were treated with SABR. SABR was associated with a lower risk of death at 6 months (HR 0.48), whereas lobectomy had better long-term survival in fit patients (HR 0.71). On propensity-score matched analysis, SABR and lobectomy had similar survivals and both had superior survival compared with conventionally fractionated irradiation (40). Similarly, a SEER study of 9,093 patients with node-negative NSCLC treated from 2003-2009 with lobectomy (79.3%), sublobar resection (16.5%), or SABR (4.2%) reported unadjusted 90-day mortality to be highest with lobectomy and lowest with SABR (4.0% *vs.* 1.3%, P=0.008). However, at 3 years, unadjusted mortality was lowest with surgery (25.0% *vs.* 45.1%, P<0.001), resulting in SABR being associated with better overall survival at 6 months but inferior long-term overall survival. Like the elderly SEER analysis, similar survival between lobectomy and SABR was seen on propensity score-matching analysis (HR 1.01, P=0.94) (41). These findings of lower acute toxicity and better 90-day mortality but inferior long-term survival with SABR compared with surgery in an unadjusted population were further confirmed in a third SEER study (42). In a systematic review of 45 publications of stage I NSCLC from 2006-2013, there was no difference at 2 years in survival (70% *vs.* 68%) or local control for 3,201 SABR patients and 2,038 surgery patients (43).

Cost-effective analyses comparing surgery and SABR for stage I NSCLC have demonstrated conflicting results. Using Medicare-allowable charge rates, one report demonstrated SABR to be less costly than surgical intervention in high risk patients, although surgery was still found to meet the standards for cost-effectiveness due to a non-significant superiority in overall survival (44). In a separate analysis using Medicare charges, SABR was found to be more cost effective for marginally operable patients, whereas lobectomy was more cost effective for clearly operable patient (45). Using Ontario, Canada fee schedules, SABR was projected to significantly reduce overall costs and surgical gains by reducing recurrences compared with conventionally fractionated radiotherapy. In that study, SABR was found to have approximately half the upfront costs of lobectomy, but lobectomy was cost effective compared with SABR by producing more QALYs at the expense of higher cost (46). Using SEER-Medicare data, SABR was found to be less costly than surgery. However, lobectomy, but not sublobar resection, was found to be cost-effective compared to SABR (47).

Given the available literature, some have suggested SABR to be a front line therapy option in operable patients who were elderly and potentially most susceptible to surgical-related complications (48). However, given that surgery has been the gold standard for all medically operable patients (49) for the past several decades, randomized data demonstrated clear rationale to warrant SABR to be considered an optimal first-line option for medically operable patients have been lacking.

STARS and ROSEL trials

In the June issue of *Lancet Oncology*, Chang and colleagues published their pooled analysis of two randomized trials comparing surgery to SABR for patients with operable stage I NSCLC (50). Their publication, the first randomized report comparing surgery and SABR for medically operable patients, combined data from the STARS (StereoTActic Radiotherapy *vs.* Surgery) international randomized phase III trial comparing CyberKnife® SABR with surgical resection and the ROSEL (Radiosurgery Or Surgery for operable Early stage non-small cell Lung cancer) VU Medical Centre Amsterdam and the Dutch Lung Cancer Research Group randomized phase III trial comparing SABR or surgery.

In the STARS trial, patient with tumors ≤4 cm and operable clinical stage I NSCLC either received surgical resection and mediastinal lymph node dissection or SABR to 54 Gy in three fractions (peripheral) or 50 Gy in

4 fractions (central). Interestingly, there was a potential bias in favor of the surgical arm in that adjuvant chemotherapy was not allowed with the SABR arm but could be given to surgery patients found to have positive margins or be upstaged to have pathological N1 or N2 disease, with adjuvant chemotherapy in this setting well established to improve overall survival (51,52). In the ROSEL trial, patients with tumors ≤3 cm with operable clinical stage IA NSCLC either received surgical resection (lobectomy was preferred but limited resection was acceptable) or SABR to 54 Gy in three fractions (peripheral) or 60 Gy in five fractions (central and tumors with broad contact to the thoracic wall). Histological confirmation of a NSCLC diagnosis was required in the STARS trial but not the ROSEL trial, although lesions had to be new or growing and radiographically consistent with NSCLC and avidity on PET/CT (50).

Although both the STARTS and ROSEL trials closed early due to poor accrual, a pooled analysis of the two trials was conducted by Chang *et al*. with a primary outcome of overall survival. Fifty-eight patients were enrolled and randomized to SABR (n=31) or surgery (n=27), with no differences in patient or tumor characteristics found between arms. Overall survival was found to be significantly higher among patients randomized to SABR (P=0.037; HR 0.14; 1-year survival 100% *vs*. 88%, 3-year survival 95% *vs*. 79%). This survival difference was significant in the STARS trial alone (P=0.0067) but not the ROSEL trial (P=0.78). The authors hypothesized that this survival difference was related to surgery resulting in worsening comorbidities after surgical reduction of lung function. This is in keeping with the Kaplan-Meier survival curves that Chang *et al*. present in image 2A, in which there is an early separation in survival in favor of SABR that is consistent with perioperative mortality from surgery, but similar survival between the two arms thereafter (50). At 3 years, there was no difference in local control (SABR 96% *vs*. surgery 100%, P=0.44), regional nodal control (90% *vs*. 96%, P=0.32), metastatic-free survival (97% *vs*. 91%, P=0.42), and recurrence-free survival (86% *vs*. 80%, P=0.54) (50).

Toxicity also generally favored the SABR arm. The lone case of treatment-related mortality occurred in the surgery cohort. In the SABR arm, no patient developed grade 4 or 5 toxicity, and 10% developed a grade 3 adverse events (6% dyspnea/cough, 10% chest wall pain, 3% fatigue, 3% rib fracture; all of these events occurred in 3 total patients). In the surgery arm, in addition to the 4% with a grade 5 toxicity, 44% developed grade 3 or 4 adverse events that included dyspnea, lung infections, chest pain, bleeding, fistula, hernia, anemia, fatigue, nausea, weight loss, and cardiac arrhythmias (50).

Given that the STARS trial only enrolled 36 of its intended 1,030 patients and the ROSEL trial only enrolled 22 of its intended 960 patients, the results reported by Chang *et al*. should be interpreted with caution, particularly the local, nodal, or distant failure rates and recurrence-free survival since follow-up was limited and so few events occurred during the study follow-up period resulting in very limited study power to detect differences between arms. Additional caution should be taken since the survival reported in the SABR arm is higher than what has generally been previously reported in SABR studies. However, this may be due to all patients receiving a SABR regimen with a biologically effective dose >100 Gy, which has previously been shown to allow for better local control and overall survival with SABR (53), and also since the current study included patients with smaller lesions, better performance statuses, fewer comorbidities, and more thorough pretreatment staging than most prior SABR reports. In contrast, only 5 of 27 patients in the surgery arm of the pooled analysis underwent a video-assisted thoracoscopic (VATs) lobectomy. It is possible that the perioperative mortality and thus overall survival for the surgery arm would have been higher had more patients underwent VATs, as has recently been demonstrated (54).

Future directions

Given the historical perception by many physicians there is lack of equipoise between the treatment modalities and given that many patients have been unwilling to undergo randomization between the two treatments that have such a different toxicity profile, trials comparing SABR and surgery will continue to have difficulty with accrual (55). The ACOSOG Z4099/RTOG 1021 randomized phase III trial of sublobar resection with or without brachytherapy versus SABR in high risk patients with stage I NSCLC, the only other phase III randomized trial conducted to date other than the STARS and ROSEL trials, is unlikely to provide any significant additional insight in the debate of SABR versus surgery given that it closed early in 2013 due to lack of accrual and is without publication. That study also differed from the STARS and ROSEL trials in calling for sublobar instead of lobar resection for surgery patients. However, additional insight from two upcoming randomized trials may be forthcoming. The VALOR trial

(Veterans Affairs Lung cancer surgery Or stereotactic Radiotherapy) is scheduled to open in the United States within the year, and the SABRTooth trial (a multicentre pilot and feasibility study that will compare SABR and surgery for peripheral stage I NSCLC in patients thought to be at higher risk of surgical complications) is also planned to open in the United Kingdom.

Conclusions

Chang and colleagues should be highly commended for a notable publication and the first phase III randomized report comparing SABR and surgery. Their findings that SABR for operative stage I NSCLC is highly effective and has a mild toxicity profile adds further credence to the notion that there is equipoise between the two treatment options and clearly supports SABR being considered a first-line option for treatment of operable stage I NSCLC.

Acknowledgements

None.

Footnote

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

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD. Available online: http://seer.cancer.gov/csr/1975_2012/. Based on November 2014 SEER data submission, posted to the SEER web site, April 2015. Accessed 28 June 2015.
3. Groome PA, Bolejack V, Crowley JJ, et al. The IASLC Lung Cancer Staging Project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007;2:694-705.
4. Bertolaccini L, Terzi A, Ricchetti F, et al. Surgery or stereotactic ablative radiation therapy: how will be treated operable patients with early stage not small cell lung cancer in the next future? Ann Transl Med 2015;3:25.
5. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
6. Dorsey JF, Kao GD, MacArthur KM, et al. Tracking viable circulating tumor cells (CTCs) in the peripheral blood of non-small cell lung cancer (NSCLC) patients undergoing definitive radiation therapy: pilot study results. Cancer 2015;121:139-49.
7. Alberts WM; American College of Chest Physicians. Diagnosis and management of lung cancer executive summary: ACCP evidence-based clinical practice guidelines (2nd Edition). Chest 2007;132:1S-19S.
8. Scott WJ, Howington J, Feigenberg S, et al. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:234S-242S.
9. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22.
10. Simone CB II, Friedberg JS, Glatstein E, et al. Photodynamic therapy for the treatment of non-small cell lung cancer. J Thorac Dis 2012;4:63-75.
11. Robinson CG, Bradley JD. The treatment of early-stage disease. Semin Radiat Oncol 2010;20:178-85.
12. Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. J Clin Oncol 2010;28:5153-9.
13. Pezzi CM, Mallin K, Mendez AS, et al. Ninety-day mortality after resection for lung cancer is nearly double 30-day mortality. J Thorac Cardiovasc Surg 2014;148:2269-77.
14. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. Ann Thorac Surg 2006;81:1013-9.
15. Rosenzweig KE, Movsas B, Bradley J, et al. ACR appropriateness criteria on nonsurgical treatment for non-small-cell lung cancer: poor performance status or palliative intent. J Am Coll Radiol 2009;6:85-95.
16. Smythe WR; American College of Chest Physicians. Treatment of stage I non-small cell lung carcinoma. Chest 2003;123:181S-187S.
17. Simone CB 2nd, Wildt B, Haas AR, et al. Stereotactic body

radiation therapy for lung cancer. Chest 2013;143:1784-90.
18. Slotman BJ, Antonisse IE, Njo KH. Limited field irradiation in early stage (T1-2N0) non-small cell lung cancer. Radiother Oncol 1996;41:41-4.
19. Bogart JA, Hodgson L, Seagren SL, et al. Phase I study of accelerated conformal radiotherapy for stage I non-small-cell lung cancer in patients with pulmonary dysfunction: CALGB 39904. J Clin Oncol 2010;28:202-6.
20. Potters L, Kavanagh B, Galvin JM, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2010;76:326-32.
21. Hurkmans CW, Cuijpers JP, Lagerwaard FJ, et al. Recommendations for implementing stereotactic radiotherapy in peripheral stage IA non-small cell lung cancer: report from the Quality Assurance Working Party of the randomised phase III ROSEL study. Radiat Oncol 2009;4:1.
22. Zou W, Yin L, Shen J, et al. Dynamic simulation of motion effects in IMAT lung SBRT. Radiat Oncol 2014;9:225.
23. Corradetti MN, Mitra N, Bonner Millar LP, et al. A moving target: Image guidance for stereotactic body radiation therapy for early-stage non-small cell lung cancer. Pract Radiat Oncol 2013;3:307-15.
24. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
25. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
26. Palma D, Senan S. Stereotactic radiation therapy: changing treatment paradigms for stage I nonsmall cell lung cancer. Curr Opin Oncol 2011;23:133-9.
27. Senan S, Palma DA, Lagerwaard FJ. Stereotactic ablative radiotherapy for stage I NSCLC: Recent advances and controversies. J Thorac Dis 2011;3:189-96.
28. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352-8.
29. Nagata Y, Hiraoka M, Shibata T, et al. A Phase II Trial of Stereotactic Body Radiation Therapy for Operable T1N0M0 Non-small Cell Lung Cancer: Japan Clinical Oncology Group (JCOG0403). Int J Radiat Oncol Biol Phys 2010;78:S27-S28.
30. Timmerman RD, Paulus R, Pass HI, et al. RTOG 0618: Stereotactic body radiation therapy (SBRT) to treat operable early-stage lung cancer patients. J Clin Oncol 2013;31:abstr 7523.
31. Haasbeek CJ, Lagerwaard FJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. J Thorac Oncol 2011;6:2036-43.
32. D'Cunha J, Herndon JE 2nd, Herzan DL, et al. Poor correspondence between clinical and pathologic staging in stage 1 non-small cell lung cancer: results from CALGB 9761, a prospective trial. Lung Cancer 2005;48:241-6.
33. Rami-Porta R, Ball D, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol 2007;2:593-602.
34. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol 2010;28:928-35.
35. Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2010;140:377-86.
36. Robinson CG, DeWees TA, El Naqa IM, et al. Patterns of failure after stereotactic body radiation therapy or lobar resection for clinical stage I non-small-cell lung cancer. J Thorac Oncol 2013;8:192-201.
37. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 2013;24:1543-8.
38. Mokhles S, Verstegen N, Maat AP, et al. Comparison of clinical outcome of stage I non-small cell lung cancer treated surgically or with stereotactic radiotherapy: results from propensity score analysis. Lung Cancer 2015;87:283-9.
39. van den Berg LL, Klinkenberg TJ, Groen HJ, et al. Patterns of Recurrence and Survival after Surgery or Stereotactic Radiotherapy for Early Stage NSCLC. J Thorac Oncol 2015;10:826-31.
40. Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. Int J Radiat Oncol Biol Phys 2012;84:1060-70.
41. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-

stage non-small cell lung cancers in the elderly. JAMA Surg 2014;149:1244-53.
42. Yu JB, Soulos PR, Cramer LD, et al. Comparative effectiveness of surgery and radiosurgery for stage I non-small cell lung cancer. Cancer 2015;121:2341-9.
43. Soldà F, Lodge M, Ashley S, et al. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic review and comparison with a surgical cohort. Radiother Oncol 2013;109:1-7.
44. Puri V, Crabtree TD, Kymes S, et al. A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: a decision analysis. J Thorac Cardiovasc Surg 2012;143:428-36.
45. Shah A, Hahn SM, Stetson RL, et al. Cost-effectiveness of stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. Cancer 2013;119:3123-32.
46. Louie AV, Rodrigues GB, Palma DA, et al. Measuring the population impact of introducing stereotactic ablative radiotherapy for stage I non-small cell lung cancer in Canada. Oncologist 2014;19:880-5.
47. Smith BD, Jiang J, Chang JY, et al. Cost-effectiveness of stereotactic radiation, sublobar resection, and lobectomy for early non-small cell lung cancers in older adults. J Geriatr Oncol 2015. [Epub ahead of print].
48. Filippi AR, Franco P, Ricardi U. Is stereotactic ablative radiotherapy an alternative to surgery in operable stage I non-small cell lung cancer? Rep Pract Oncol Radiother 2014;19:275-9.
49. Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. J Clin Oncol 2014;32:2847-54.
50. 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.
51. NSCLC Meta-analyses Collaborative Group, Arriagada R, Auperin A, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010;375:1267-77.
52. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719-27.
53. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100.
54. Chen FF, Zhang D, Wang YL, et al. Video-assisted thoracoscopic surgery lobectomy versus open lobectomy in patients with clinical stage I non-small cell lung cancer: a meta-analysis. Eur J Surg Oncol 2013;39:957-63.
55. Loo BW Jr. Stereotactic ablative radiotherapy (SABR) for lung cancer: What does the future hold? J Thorac Dis 2011;3:150-2.

Cite this article as: Simone CB 2nd, Dorsey JF. Additional data in the debate on stage I non-small cell lung cancer: surgery versus stereotactic ablative radiotherapy. Ann Transl Med 2015;3(13):172. doi: 10.3978/j.issn.2305-5839.2015.07.26

Current Evidence

Stereotactic ablative radiotherapy: aim for a cure of cancer

Joe Y. Chang

Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

Correspondence to: Joe Y. Chang, MD, PhD. Professor, Clinical Section Chief, Thoracic Radiation Oncology; Director, Stereotactic Ablative Radiotherapy Program, Department of Radiation Oncology, MD Anderson Cancer Center, Unit 97, 1515 Holcombe Blvd., Houston, TX 77030, USA. Email: jychang@mdanderson.org.

Submitted Nov 14, 2014. Accepted for publication Nov 14, 2014.
doi: 10.3978/j.issn.2305-5839.2014.11.17
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2014.11.17

Stereotactic ablative radiotherapy (SABR) differs from conventional radiation in several ways (*Figure 1*). It delivers a high radiation dose to the target that can potentially eliminate cancer. It is typically used to treat smaller tumors that have been detected early. SABR is guided by a special imaging system such as computerized tomography or computed tomography (CT). The CT is built into the radiation treatment machine. Because CT scanning can accurately pinpoint a tumor, SABR is able to give higher doses of radiation directly to the tumor without damaging nearby critical normal structures. Higher treatment doses are given in a much shorter period of time typically three to five treatments over a period of 5 days whereas typical conventional radiation therapy is given 30 minutes a day for 6 weeks or more.

Figure 1 Stereotactic ablative radiotherapy: aim for a cure of cancer (1). Available online: http://www.asvide.com/articles/410

SABR can be used for early stage lung cancer (2-7), lung cancer that has returned, multiple primary lung cancer (5), early stage liver cancer, prostate cancer, and also other cancers that have recurred (8) and or spread. MD Anderson has treated thousands of patients with SABR for more than 10 years. For early stage cancer, SABR is a possible cure. Because SABR is more precise compared to conventional radiation therapy and the treatment area is smaller, most patients have very few side effects (7). Severe side effects are very rare.

The minimal side effects and shorter treatment time are just a few of the benefits. SABR has shown a very high tumor control rate with a significantly improved cure rate for nonsurgical patients who have early stage non-small cell lung cancer. In simple terms, SABR has been proven to be a very effective treatment.

Lung cancer can be difficult to treat because it is often discovered in later stages. In many cases, treatment is not very effective. The five-year survival rate for lung cancer is only 15%. MD Anderson wants to change these statistics. We have a lung cancer screening program for high risk patients. These are patients who are over 55 years of age and have been chronic smokers over one pack of cigarettes a day for 30 years. The goal is to find early stage lung tumors while they're still small and curable. In some cases, individuals with cancer enter into a clinical trial for treatment. A clinical trial is a process to find a better way to treat a specific type of cancer. MD Anderson offers clinical trials that compare the success of SABR to other types of cancer treatment including but not limited to, those for lung cancer. Most patients treated with SABR are reaching high survival rates for early stage lung cancer. If early stage lung cancer could be identified sooner and treated with SABR, it's possible that up to 70-80% of lung cancer could be cured. The result of SABR is comparable

with surgical resection (2,6).

Acknowledgements

Disclosure: The author declares no conflict of interest.

References

1. Chang JY. Stereotactic ablative radiotherapy: aim for a cure of cancer. Asvide 2015;2:001. Available online: http://www.asvide.com/articles/410
2. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. JAMA Surg 2014. [Epub ahead of print].
3. Li Q, Swanick CW, Allen PK, et al. Stereotactic ablative radiotherapy (SABR) using 70Gy in 10 fractions for non-small cell lung cancer: Exploration of clinical indications. Radiother Oncol 2014;112:256-61.
4. Chang JY, Li QQ, Xu QY, et al. Stereotactic ablative radiation therapy for centrally located early stage or isolated parenchymal recurrences of non-small cell lung cancer: how to fly in a "no fly zone". Int J Radiat Oncol Biol Phys 2014;88:1120-8.
5. Chang JY, Liu YH, Zhu Z, et al. Stereotactic ablative radiotherapy: a potentially curable approach to early stage multiple primary lung cancer. Cancer 2013;119:3402-10.
6. Shirvani SM, Chang JY, Roth JA. Can stereotactic ablative radiotherapy in early stage lung cancers produce comparable success as surgery? Thorac Surg Clin 2013;23:369-81.
7. Chang JY, Liu H, Balter P, et al. Clinical outcome and predictors of survival and pneumonitis after stereotactic ablative radiotherapy for stage I non-small cell lung cancer. Radiat Oncol 2012;7:152.
8. Liu H, Zhang X, Vinogradskiy YY, et al. Predicting radiation pneumonitis after stereotactic ablative radiation therapy in patients previously treated with conventional thoracic radiation therapy. Int J Radiat Oncol Biol Phys 2012;84:1017-23.

Cite this article as: Chang JY. Stereotactic ablative radiotherapy: aim for a cure of cancer. Ann Transl Med 2015;3(1):12. doi: 10.3978/j.issn.2305-5839.2014.11.17

Current Evidence

Local control rates with five fractions of stereotactic body radiotherapy for primary lung tumors: a single institution experience of 153 consecutive patients

Deepinder Singh, Yuhchyau Chen, Derek P. Bergsma, Kenneth Y. Usuki, Sughosh Dhakal, Mary Z. Hare, Neil Joyce, Therese Smudzin, Doug Rosenzweig, Michael C. Schell, Michael T. Milano

Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Contributions: (I) Conception and design: D Singh, M Milano; (II) Administrative support: L Finger; (III) Provision of study materials or patients: D Rosenzweig, D Singh; (IV) Collection and assembly of data: D Singh, T Smudzin; (V) Data analysis and interpretation: M Milano, T Smudzin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Deepinder Singh, MD. Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Ave, Box 647, Rochester, NY 14642, USA. Email: deepinder_singh@urmc.rochester.edu.

Background: We report our institutional experience with stereotactic body radiotherapy (SBRT) for treatment of non-small cell lung cancer (NSCLC).

Methods: One hundred and fifty-three consecutive patients diagnosed with NSCLC were treated with image-guided SBRT between 2008 and 2012. Stage I patients were treated in lieu of resection, stage II-III patients were not candidates for concurrent chemoradiation and had disease amenable to SBRT and stage IV patients had oligometastatic disease. The median prescribed isocenter dose was 50 Gy in five fractions (range, 40-60 Gy) with the majority (n=121) receiving 50 Gy in five fractions. The 80% isodose line covered the planning target volume (PTV) [defined as gross tumor volume (GTV) + 7-11 mm volumetric expansion). Follow-up ranged from 1-46 months with a median of 13 months.

Results: The 1- and 2-year local control (LC) rates for all patients were 92% and 85% respectively. For 111 patients with stage I NSCLC, 1- and 2-year LC was 95% and 85%, with all local recurrence (LR) occurring within 2 years. LC at 1- and 2-year was 87% for both stage II (n=19) and stage III (n=14), with all LR occurring within 10 months. For oligometastatic stage IV (n=9) patients, LC at 1- and 2-year was 71%, with all LR occurring within 5 months. Two-year LC among patients with tumors <1 cm was 100% compared to 84% for those with tumor size >1 cm. Tumor histology, prescribed dose, patient age, and prior radiotherapy (RT) or surgery had no significant impact on LC rates. Prior chemotherapy had a significant negative impact on LC with 1- and 2-year LC of 59%, compared to 1- and 2-year LC of 93% and 85%, respectively (P=0.015). n multivariate analysis, stage was the only significant predictor of LC. Among stage I NSCLC patients, 6 of 111 developed LR, 13 developed distant failures (of whom 5 also developed LR). Of these 111 patients, 5 died from NSCLC and 2 died from causes other than NSCLC; no patient died from treatment-related toxicity.

Conclusions: SBRT plays a vital role and offers excellent LC in medically-inoperable NSCLC patients, with treatment during the early stage of the disease determined as the single most significant predictor of LC on multivariate analysis.

Keywords: Non-small cell lung cancer (NSCLC); radiation therapy; stereotactic body

Submitted Jul 06, 2015. Accepted for publication Jul 29, 2015.

doi: 10.3978/j.issn.2218-676X.2015.08.01

View this article at: http://dx.doi.org/10.3978/j.issn.2218-676X.2015.08.01

Introduction

Lung cancer remains the number one cause of cancer mortality in both men and women in the United States, despite tremendous improvement in diagnostic as well as therapeutic modalities (1). Only 20% of patients with non-small cell lung cancer (NSCLC) present with early stage or localized disease, although proposed lung cancer screening programs are likely to lead to a relative increase in early stage NSCLC (2). Surgical resection for localized early stage NSCLC remains the standard of care for early stage NSCLC and yields a 5-year survival rate of 60-70% in operable patients. However, surgery is often infeasible or may involve excessive risk for patients with severe co-morbid tobacco-related cardiopulmonary disease or who decline surgery for personal reasons (3). Observation is not typically recommended; as most will die from progressive lung cancer rather than co-morbid diseases (4). Radiotherapy (RT) remains the standard nonsurgical option for early stage lung cancer. However, conventional fractionated radiotherapy (CFRT) delivering 45-66 Gy in 1.8-2.0 Gy fractions has yielded dismal results (5-year survival rate of 10-30%), with the best results seen when local control (LC) is achieved and/or with the delivery of greater doses (5,6).

Early-stage NSCLC is not inherently systemic from diagnosis, but poor LC with conventional daily fractionated RT has led to the development of nonsurgical approaches aimed at increasing survival by improving local tumor ablation (7). Stereotactic body radiotherapy (SBRT) has been developed as a novel modality for early stage NSCLC and has emerged as standard treatment option for medically-inoperable patients. SBRT uses a large number of non-opposing, often non-coplanar beams, with anatomic targeting using a variety of image-guidance radiotherapy (IGRT) modalities to improve target localization (8,9). The potential benefits of SBRT include non-invasive outpatient treatment without the risks associated with surgery, and increased convenience compared to conventional daily RT (10). The initial single institutional, as well as multi-institutional clinical trials, have shown LC rates as high as 98% at 3 years in early stage lung cancer with low incidence of long-term toxicity (3). With SBRT, improved LC rates are achieved which are almost twice as high as would be expected with conventional 6-7 weeks of daily RT. Despite encouraging early results, long-term follow up and evaluation of these patients is required to understand long term control rates and patterns of recurrence, as well as the type, timing, and severity of late toxicities. SBRT offers promising progression free survival rates without significant increased toxicity compared with standard techniques (3,7-12).

While SBRT seems as efficacious as surgical resection (3,13-16), sufficient outcome data comparing these two modalities are lacking. Three phase III studies comparing SBRT *vs.* surgery in patients with early stage NSCLC were prematurely closed due to slow accrual: the MDACC (stereotactic RT *vs.* surgery) STARS trial [NCT00840749], the Dutch Radiosurgery or Surgery for Early stage Lung cancer (ROSEL) trial [NCT00687986], and the American College of Surgeons cooperative group trial [NCT01336894]. A recently published pooled analysis of 58 patients from the STARS and ROSEL studies suggested possibly improved 1-year and 3-year overall survival (OS) in SBRT *vs.* surgery arms, but no significant difference in frequency of local, regional, or distant metastases or recurrence-free survival between the treatment groups (13). As discussed above, SBRT has clearly resulted in superior outcomes *vs.* conventionally fractionated RT, but whether this would be true with modern staging and treatment approaches is unknown. Findings from population-based studies and propensity matched analysis comparing outcomes of SBRT *vs.* surgery have shown similar OS and disease specific survival (14,15). The Scandinavian "Stereotactic Precision and Conventional Radiotherapy Evaluation" (SPACE) study which randomized ~102 patients of SBRT (66 Gy in 3 fractions) to conventional RT (70 Gy in 35 fractions) recently closed to accrual (NCT01920789). The Trans-Tasman "Hypofractionated Radiotherapy (Stereotactic) *vs.* Conventional Radiotherapy for Inoperable Early Stage I Non-small Cell Lung Cancer" (CHISEL) is enrolling patients in a phase III study of SBRT (54 Gy in 3 fractions) *vs.* conventional radiation therapy (60-66 Gy in 30-33 fractions) (NCT01014130).

The current retrospective study was undertaken to evaluate our institutional results for high-dose SBRT for early stage NSCLC since we began using a five fraction treatment regimen. We sought to better characterize tumor control with a prescribed dose of 50-60 Gy and determine if outcomes from our single institution with a large cohort of patients were comparable to those of published SBRT data.

Patients and methods

Between January 2008 and December 2012, 153 consecutive patients diagnosed with NSCLC were treated with image-guided SBRT. The study was approved by the University of Rochester Medical Center Research Subjects Review Board.

Patient population

Eligibility criteria included patients with newly diagnosed NSCLC, age >18, Karnofsky performance status >70, CT-defined tumor diameter <5 cm, and no other active metastatic sites outside the lungs. All patients were deemed ineligible for surgical resection, or had refused surgery for personal reasons. The work-up included pulmonary function test, contrast enhanced CT of the chest and abdomen and/or FDG-PET/CT, as well as tissue confirmation in the majority of patients. Patients were followed with CT or PET-CT every 3-6 months for post-treatment surveillance. Patients found to have metachronous NSCLC on surveillance imaging were allowed to undergo additional SBRT treatments.

SBRT technique

The SBRT techniques described in detail in previous publications from our group are briefly summarized here (17,18). All patients undergoing initial CT simulation required immobilization with a vacuum cushion device. All patients were treated with the Novalis ExacTrac system (Brain Lab Inc.). The ExacTrac patient positioning platform using infrared reflecting body fiducial markers monitored by two ceiling mounted infrared cameras was used for patient positioning and real-time monitoring. Respiratory motion was minimized by using relaxed expiratory breath hold techniques (in most patients) or shallow breathing (in patients with poor lung function). Patients also underwent a verification CT in the set-up position, which was fused to the planning CT, prior to treatment and after the second fraction to ensure three-dimensional set-up accuracy. The gross tumor volume (GTV) was delineated using CT and fused PET imaging in the majority of cases. The use of arcs and non-coplanar beams was encouraged. Dose volume histograms (DVH) were calculated for the lung (defined as total lung minus GTV), heart, esophagus, spinal cord, and liver. The planning target volume (PTV) was generated using a 7 mm circumferential and 11 mm superior-inferior expansion of the GTV (with no expansion for CTV). The 80% isodose line encompassed the PTV, with isocenter dose defined as 100% of the prescribed dose. The prescribed target dose was determined based on the DVH of normal (uninvolved) lung and surrounding organs. The median prescription dose was 50 Gy in five fractions (range, 40-60 Gy) to isocenter with 80-100% isodose covering 99-100% of PTV. Generally, 95% of the PTV was covered by the 85-95% isodose line. Patients were required to have 1,000 mL of tumor free lung, with a volume of lung receiving >20 Gy (V20) less than 12%. The spinal cord maximum was required to be <4.5 Gy/fraction. Care was taken so that hot spots (i.e., >95% isodose) occurred solely within the GTV. The dose for smaller peripheral tumors was mostly 50-60 Gy and the dose for larger central tumors was mostly 40-50 Gy.

Outcomes/statistics

The primary end point was tumor LC and secondary end points included regional control as well as OS. Actuarial tumor control and survival were calculated using Kaplan-Meier actuarial survival analyses. OS was defined from date of completion of SBRT until death or last follow-up. Patient LC was scored as an event if any treated lesion grew by ≥20% based on the Response Evaluation Criteria In Solid Tumors (RECIST), or a local recurrence (LR) was pathologically confirmed. LC was analyzed per patient, meaning that if a patient had more than one lesion treated, progression of any of the treated lesions was considered a LR. LC was analyzed by tumor size among patients with more than one lesion, treated tumor size represents the largest lesion treated. Among patients who underwent repeat courses of SBRT for new lesions(s), only the LC of the index lesion(s) was considered in this study. Stata version 9.2 was used for all data analysis.

Results

Patient characteristics

There were 74 males and 79 females. The median age was 75 years (range, 50-97 years). Thirty-eight patients had previous thoracic surgery, 36 had previous thoracic RT and 10 had received systemic chemotherapy in the past (*Table 1*). Cardiopulmonary co-morbidity was the most common factor for medical inoperability in patients with otherwise technically resectable tumors.

Tumor characteristics

The majority of patients (n=116) underwent bronchoscopic or CT-guided biopsy for tissue diagnosis; however, 17 patients (11%) were considered to be poor risk candidates or refused biopsy for personal reasons. Among the 116 biopsy proven NSCLC, tumor histologies included

Table 1 Patient characteristics

Characteristics	Number (%)
Median age	75
Range	50-97
Gender	
Male	74 (48.4)
Female	79 (51.6)
Previous treatment (no/yes)	
Surgery	115/38
RT	117/36
Chemotherapy	143/10
Co-morbidities	
Pulmonary	100 (65.0)
Cardiac	5 (2.0)
None	48 (31.0)

RT, radiotherapy.

Table 2 Tumor characteristics

Characteristics	Number (%)
Histology	
Adenocarcinoma	73 (47.7)
Squamous cell carcinoma	36 (23.5)
Bronchoalveolar carcinoma	10 (6.5)
Large cell carcinoma	3 (1.9)
Poorly differentiated carcinoma not otherwise specified	14 (9.2)
No tissue Dx	17 (11.1)
Size (mm)	
≤10	11 (7.1)
11-20	84 (54.9)
21-30	36 (23.5)
31-40	21 (13.7)
41-50	1 (0.7)
Stage	
I	111 (72.5)
II	19 (12.4)
III	14 (9.1)
IV	9 (5.9)
Location	
Peripheral	138 (90.0)
Central/paraspinal	15 (10.0)

adenocarcinoma (n=73, 54%), squamous cell carcinoma (n=36, 26%), bronchoalveolar carcinoma (n=10, 7%), large cell carcinoma (n=3, 1.9%), and poorly differentiated carcinoma not otherwise specified (n=14, 10%) (*Table 2*).

Tumor size (the largest dimension of the largest target if more than one lesion was treated) was distributed as follows: <10 mm (n=11, 7%); 11-20 mm (n=84, 54%); 21-30 mm (n=36, 23%); 31-40 mm (n=21, 14%); >41 mm (n=1) (*Table 2*). A total of 72% (n=111) of patients had stage I disease, 12% (n=19) had stage II disease, 9% (n=14) had stage III disease, and 6% (n=9) had stage IV disease (*Table 2*). Peripherally located tumors accounted for 90% (n=138) of patients *vs.* 10% (n=15) which were central or paraspinal in location.

Local tumor response

The 1- and 2-year LC rates for all patients were 92% and 85% respectively (*Figure 1*). For 111 patients with stage I NSCLC, 1- and 2-year LC was 95% and 85%, with all LR occurring within 2 years. LC at 1- and 2-year was 87% for both stage II (n=19) and stage III (n=14) patients, with all LR occurring within 10 months (*Figure 2*). The 1-year and 2-year LC for oligometastatic stage IV (n=9) patients were 71% each, with all LR occurring within 5 months. The 2-year LC rate among patients with tumors <1 cm was 100% compared to 84% for those with tumor size >1 cm. Tumor histology, prescribed dose, patient age, and prior RT or surgery had no significant impact on LC rates. Prior chemotherapy had a significant negative impact on LC with 1- and 2-year LC of 59% compared to 1- and 2-year LC of 93% and 85%, respectively (P=0.015). However, on multivariate analysis, NSCLC stage was the single most significant factor for LC (P=0.048).

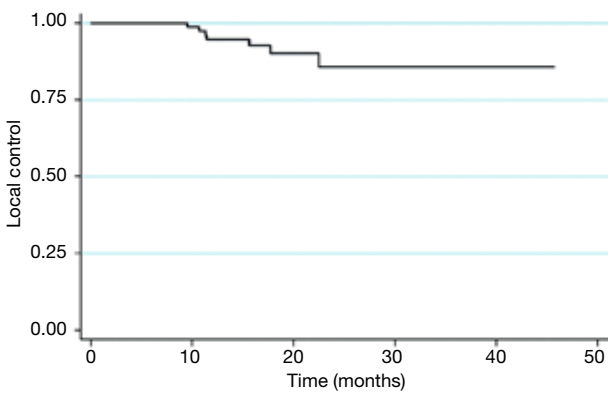


Figure 1 Overall local control (LC) for all patients: 92% at 1 year and 85% at 2 years.

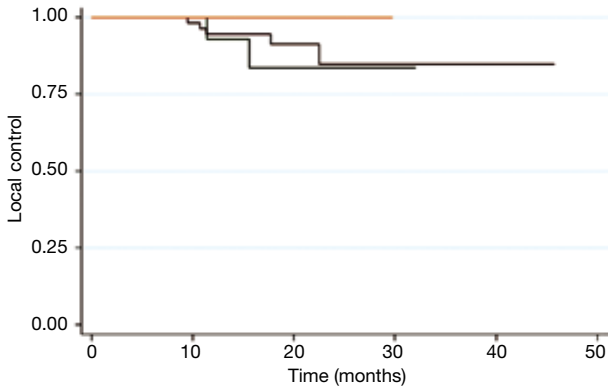


Figure 2 Local control (LC) rates at 1 year: ≤10 mm lesions 100%, 21-30 mm lesions 95%, 31-40 mm lesions 93%. LC rates at 2 years: ≤10 mm lesions 100%, 21-30 mm lesions 85%, 31-40 mm lesions 84%.

Recurrence

Among the 111 stage I NSCLC patients there were six cases of LR, of which five also developed distant recurrence, as well as an additional eight cases of distant recurrence without LR. Of these 111 patients, five died from NSCLC and two died from causes other than NSCLC.

Toxicity disease

All patients tolerated the SBRT very well. Thirteen patients needed to be treated with steroid inhalers and oral steroids for a short duration. No patient died from treatment-related toxicity.

Discussion

Lung cancer remains one of the most lethal cancers in both men and women in the United States, and accounts for 30% of all cancer deaths (1). Only 20-25% patients with NSCLC patients present with early stage or are deemed to have localized disease. Surgery still remains the standard of care with a 5-year survival rate of 65% seen in stage I patients, along with a 5-year LC rate of 78% (16,19-21).

There are no large published randomized studies comparing SBRT and surgery for operable patients for early stage disease (13) and three phases III randomized studies that were initiated to compare SBRT with surgery in patients with early stage NSCLC were closed early due to slow accrual. These include (I) the STAR trial [NCT00840749], looking at SBRT with Cyber Knife delivering a dose of receive 60 Gy in three fractions to peripheral tumors, and 60 Gy in four fractions to central tumors *vs.* surgery for stage IA or IB patients (maximum diameter <4 cm); (II) the ROSEL trial [NCT00687986], a Dutch multi-center randomized study of gantry-based SBRT *vs.* surgery for peripheral stage IA NSCLC; and (III) the ACOSOG trial [NCT01336894]. Although a recently published study with only 58 patients treated either with SABR (n=31) or lobectomy (n=27) showed results in favor of SBRT over surgery (3 years OS and RFS of 95% and 86% for SABR and 79% and 80% for surgery respectively) (13), we are still waiting for the mature data, and in the meantime surgery remains the standard of care (21). The pooled analysis of the STAR and ROSEL trials showed promising estimated OS at 1- and 3-year of 100% and 95% in the SABR group and 86% and 79% in the surgical group (P=0.037), but did not show any significant difference in frequency of local, regional, or distant failure as at 3 years, 96% of patients in the SABR group were free from LR compared with 100% patients with patients in the surgery group (P=0.44) (13).

Initial published phase I and phase II studies from Indiana University showed promising results using SBRT in early stage NSCLC (22-24). In a subsequent update, they reported Kaplan-Meier LC of 88.1% at 3 years, median survival (MS) of 32.4 months, and 3-year OS of 42.7% [95% confidence interval (CI), 31.1-54.3%] at a median follow-up of 50.2 months. For T1 and T2 tumors MS was 38.7 and 24.5 months, respectively, with cancer-specific survival (CSS) at 3 years being 81.7% (25). Baumann *et al.* reported a 3-year LC rate of 92%, with OS of 86%, 65%, 60%, and CSS of 93%, 88%, and 88% at 1, 2, and 3 years respectively (11).

Review of our institutional experience with five fraction SBRT shows that the 1-, 2-, and 5-year LC rates were 98%, 90%, and 88% respectively; and specifically for 106 patients with stage I NSCLC, 1- and 2-year LC was 95% and 85%. Traditionally, we have been prescribing the SBRT dose to the isocenter with a median prescription dose of 50 Gy in five fractions (range, 40-60 Gy) with 80-100% isodose covering 95% of PTV. Our study shows excellent control rates comparable to other studies, although the total dose in our study is less than other authors who prescribe dose to a volume or to the isocenter (3,26,27). In addition to the excellent control rates with lower total doses of SBRT, our patients did not experience any significant acute or late grade III/IV radiation toxicity.

Onishi *et al.* published a large retrospective review of 257 stage I resectable patients from 14 centers in Japan showing 5-year actuarial LC rates of 84% for patients treated with

SBRT receiving a BED of 100 Gy or more (based on assumed tumor a/b of 10), and 37% for those receiving less than 100 Gy. This dose-response relationship corroborates with that seen with conventionally fractionated radiation. There was no difference in the LR rates of squamous cell carcinoma and adenocarcinoma with a 71% 5-year OS for medically operable patients receiving the higher dose range with relatively low rates of radiation toxicity (3,26). In our current study, the BED doses ranged from 72-100 Gy for central tumors (n=15, 10%) and 96-132 Gy BED (n=138, 90%) for peripheral tumors with no statistically significant differences in LC rates. One possible explanation could be the limited number of patients with central tumors.

In order to determine predictors of LC and OS, many authors have looked at tumor location in the chest, T stage, GTV, histology, laterality, pulmonary function tests, sex, age, cardiac *vs.* pulmonary cause of inoperability, oxygen dependence, performance status at treatment, ongoing smoking, and PTV. There was no factor significantly predicting OS in the univariate analysis, although some authors pointed out that T size was important (24); however, a subsequent study from their center showed that the tumor size did not have significant impact on survival (P=0.712) (25). Tumor histology, prescribed dose, patient age, and prior RT or surgery had no significant impact on LC rates. However, progression of disease affected OS and CSS negatively (P<0004, and P<0.00001 respectively).

In a series by Fakiris and colleagues from Indiana University, the regional (nodal) and distant recurrence occurred in 6 (8.6%) and 9 patients (12.9%), respectively (25). Onishi *et al.* reported that LR, lymph node metastases, and distant metastases occurred in 8 (9.2%), 13 (14.9%), and 19 cases (21.8%), respectively (27). Among our stage I NSCLC patients, 6 of 111 developed LF, and 13 developed distant failure (of whom 5 also developed LF). Of these 111 patients, 5 died from NSCLC and 2 died from causes other than NSCLC. Nath *et al.* reported nodal failures in 3 of 46 evaluable patients (7%) with actuarial 24-month nodal control being 91% (95% CI, 81-100%), and the cumulative incidence of nodal failure being 6% at 24 months. Factors thought to be potentially associated with nodal failure showed no variables associated with nodal control including use of PET imaging (P=0.61), dose per fraction (P=0.89), lesion position (P=0.89), histology (P=0.72), and lesion size (P=0.16) (9).

There was no significant survival difference between patients with peripheral *vs.* central tumors (MS 33.2 *vs.* 24.4 months, P=0.697). Grade 3 to 5 toxicity occurred in 5 of 48 patients with peripheral lung tumors (10.4%) and in 6 of 22 patients (27.3%) with central tumors (25). Chang *et al.* treated a series of 27 centrally or superiorly located lesions with a slightly more modest dose of 40-50 Gy in four fractions. At a median of 17 months, there was no LR seen in the 20 patients receiving 50 Gy (BED 112.5 Gy). There were three cases of grade 2-3 skin/chest wall toxicity and one brachial plexopathy related to a large volume of plexus receiving 40 Gy. However, there was no observed grade 3 pulmonary or esophageal toxicity (28). Our patients tolerated SBRT very well. Thirteen of our patients needed to be treated with steroid inhalers/oral steroids for a short duration. There was no grade III-V toxicity. One patient was noted to have a rib fracture that was treated with analgesics alone.

We used SBRT to treat stage II or III patients, as well some metachronous/oligometastatic lesions, not amenable to surgery or chemotherapy (7). Our studies showed an excellent LC rate of 87% for both stage II and III at 1 and 2 years. The LFs were seen around 10 months in these groups. The 1- and 2-year LC for stage IV were 71% each. Treatment of locally advanced or even metastatic NSCLC with SBRT combined with medical therapies is an area of interest with several institutional studies investigating its use as primary or oligometastatic tumor control in combination with adjuvant chemotherapy [NCT01899989] or even concurrent targeted molecular agents (29). Memorial Sloan-Kettering Cancer Center is currently enrolling patients on a phase I dose escalation study to determine the maximum tolerated dose of SBRT to gross tumor followed by chemotherapy for stage IIA-IIIA NSCLC [NCT01711697].

The RTOG has performed several non-randomized clinical trials investigating the safety and efficacy of SBRT in both inoperable and operable patients. RTOG 0236 was a phase II trial enrolling medically inoperable patients with early stage NSCLC outside the zone of the proximal tracheobronchial tree treated with SBRT to a dose of 60 Gy in three fractions without heterogeneity corrections. Outcomes were excellent with a remarkable 97.6% primary tumor control at median follow up of 34.4 months among 55 evaluable patients (30). A recent 5-year update confirmed excellent primary control of 93% as well as involved lobar control of 80%; however, regional and distant failure remained significant issues with 26% DFS and 40% OS (31). More recently, RTOG 0618 enrolled medically operable patients with similar early stage NSCLC tumors treated with the same SBRT technique yielding an excellent primary tumor control of 92.7%; however, involved lobar

control was unexpectedly low at 80.8% at 2 years (32). As the preceding RTOG trials excluded tumors located within the proximal tracheobronchial tree due to concern for risk for severe toxicity, RTOG 0813 was implemented as a dose escalation study to determine the maximum tolerated dose of SBRT when treating tumors within the proximal tracheobronchial tree or adjacent to mediastinal or pericardial pleura. The starting fractional dose was 10 Gy with an increase in 0.5 Gy increments up to 12 Gy over a total course of five fractions [NCT00750269].

In general, limitations of our study include being retrospective in nature as well as marked variation in terms of tumor primary site, size, and histology. Because the majority (90%) of patients were treated with the same dose (60 Gy in five fractions), and the dose range was not large due to smaller number in the 40-50 Gy in five fractions group, we could not adequately analyze a dose-response relationship. Nevertheless, we are able to report promising LC and survival outcomes in this cohort of patients treated with NSCLC with five fractions of SBRT.

Conclusions

SBRT using Novalis/4D techniques for primary lung cancer seems to be very safe and well tolerated, with no grade III/IV toxicity in our study. It offers excellent LC in medically-inoperable NSCLC patients, with treatment during the early stage of the disease determined as the most significant predictor of LC on multivariate analysis.

Acknowledgements

We thank Mrs. Laura Finger for editorial assistance.

Footnote

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

References

1. American Cancer Society. What are the key statistics about lung cancer? Available online: http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics
2. Henschke CI, Yip R, Yankelevitz DF, et al. Definition of a positive test result in computed tomography screening for lung cancer: a cohort study. Ann Intern Med 2013;158:246-52.
3. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100.
4. McGarry RC, Song G, des Rosiers P, et al. Observation-only management of early stage, medically inoperable lung cancer: poor outcome. Chest 2002;121:1155-8.
5. Sibley GS, Jamieson TA, Marks LB, et al. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. Int J Radiat Oncol Biol Phys 1998;40:149-54.
6. Dosoretz DE, Galmarini D, Rubenstein JH, et al. Local control in medically inoperable lung cancer: an analysis of its importance in outcome and factors determining the probability of tumor eradication. Int J Radiat Oncol Biol Phys 1993;27:507-16.
7. Salazar OM, Sandhu TS, Lattin PB, et al. Once-weekly, high-dose stereotactic body radiotherapy for lung cancer: 6-year analysis of 60 early-stage, 42 locally advanced, and 7 metastatic lung cancers. Int J Radiat Oncol Biol Phys 2008;72:707-15.
8. Martin A, Gaya A. Stereotactic body radiotherapy: a review. Clin Oncol (R Coll Radiol) 2010;22:157-72.
9. Nath SK, Sandhu AP, Kim D, et al. Locoregional and distant failure following image-guided stereotactic body radiation for early-stage primary lung cancer. Radiother Oncol 2011;99:12-7.
10. Walsh J. Stereotactic Body Therapy Radiation for the Treatment of Early Stage Non Small Cell Lung Cancer. Available online: http://www.medscape.com/viewarticle/748968
11. Baumann P, Nyman J, Lax I, et al. Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer. A retrospective analysis of patients treated in the Nordic countries. Acta Oncol 2006;45:787-95.
12. Beitler JJ, Badine EA, El-Sayah D, et al. Stereotactic body radiation therapy for nonmetastatic lung cancer: an analysis of 75 patients treated over 5 years. Int J Radiat Oncol Biol Phys 2006;65:100-6.
13. 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.
14. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either

stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 2013;24:1543-8.
15. Palma D, Visser O, Lagerwaard FJ, et al. Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery. Radiother Oncol 2011;101:240-4.
16. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol 2010;28:928-35.
17. Okunieff P, Petersen AL, Philip A, et al. Stereotactic Body Radiation Therapy (SBRT) for lung metastases. Acta Oncol 2006;45:808-17.
18. Singh D, Chen Y, Hare MZ, et al. Local control rates with five-fraction stereotactic body radiotherapy for oligometastatic cancer to the lung. J Thorac Dis 2014;6:369-74.
19. Nesbitt JC, Putnam JB Jr, Walsh GL, et al. Survival in early-stage non-small cell lung cancer. Ann Thorac Surg 1995;60:466-72.
20. Kelsey CR, Boyd JA, Hubbs JL, et al. Local/regional recurrence following surgery for early-stage lung cancer: a 10-year experience with 975 patients. J Clin Oncol 2008;26:7542.
21. Ettinger DS, Akerley W, Borghaei H, et al. Non-small cell lung cancer. J Natl Compr Canc Netw 2012;10:1236-71.
22. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 2003;124:1946-55.
23. McGarry RC, Papiez L, Williams M, et al. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. Int J Radiat Oncol Biol Phys 2005;63:1010-5.
24. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
25. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75:677-82.
26. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004;101:1623-31.
27. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352-8.
28. Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;72:967-71.
29. Iyengar P, Kavanagh BD, Wardak Z, et al. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. J Clin Oncol 2014;32:3824-30.
30. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
31. Timmerman R, Paulus R, Galvin J, et al, RTOG 0236: Stereotactic body radiation therapy (SBRT) to treat medically inoperable early stage lung cancer patients: American Society for Therapeutic Radiology and Oncology (ASTRO) Annual Meeting, Chicago, IL. Int J Radiat Oncol Biol Phys 2009;75:S3.
32. Timmerman RD, Paulus R, Pass HI, et al. RTOG 0618: Stereotactic body radiation therapy (SBRT) to treat operable early-stage lung cancer patients. J Clin Oncol 2013;31:abstr 7523.

Cite this article as: Singh D, Chen Y, Bergsma DP, Usuki KY, Dhakal S, Hare MZ, Joyce N, Smudzin T, Rosenzweig D, Schell MC, Milano MT. Local control rates with five fractions of stereotactic body radiotherapy for primary lung tumors: a single institution experience of 153 consecutive patients. Transl Cancer Res 2015;4(4):332-339. doi: 10.3978/j.issn.2218-676X.2015.08.01

Local control rates with five-fraction stereotactic body radiotherapy for oligometastatic cancer to the lung

Deepinder Singh, Yuhchyau Chen, Mary Z. Hare, Kenneth Y. Usuki, Hong Zhang, Thomas Lundquist, Neil Joyce, Michael C. Schell, Michael T. Milano

Department of Radiation Oncology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, USA

Correspondence to: Deepinder Singh, MD. Department of Radiation Oncology, University of Rochester, 601 Elmwood Ave, Box 647, Rochester, NY 14642, USA. Email: deepinder_singh@urmc.rochester.edu.

Objective: To report our institutional experience with five fractions of daily 8-12 Gy stereotactic body radiotherapy (SBRT) for the treatment of oligometastatic cancer to the lung.

Methods: Thirty-four consecutive patients with oligometastatic cancers to the lung were treated with image-guided SBRT between 2008 and 2011. Patient age ranged from 38 to 81 years. There were 17 males and 17 females. Lung metastases were from the following primary cancer types: colon cancer (n=13 patients), head and neck cancer (n=6), breast cancer (n=4), melanoma (n=4), sarcoma (n=4) and renal cell carcinoma (n=3). The median prescription dose was 50 Gy in five fractions (range, 40-60 Gy) to the isocenter, with the 80% isodose line encompassing the planning target volume (PTV) [defined as gross tumor volume (GTV) + 7-11 mm volumetric expansion]. The follow-up interval ranged from 2.4-54 months, with a median of 16.7 months.

Results: The 1-, 2-, and 3-year patient local control (LC) rates for all patients were 93%, 88%, and 80% respectively. The 1-, 2-, and 3-year overall survival (OS) rates were 62%, 44%, and 23% respectively. The 1- and 2-year patient LC rates were 95% and 88% for tumor size 1-2 cm (n=25), and 86% for tumor size 2-3 cm (n=7). The majority (n=4) of local failures occurred within 12 months. No patient experienced local failure after 12 months except for one patient with colon cancer whose tumors progressed locally at 26 months. All five patients with local recurrences had colorectal cancer. Statistical analyses showed that age, gender, previous chemotherapy, previous surgery or radiation had no significant effect on LC rates. No patient was reported to have any symptomatic pneumonitis at any time point.

Conclusions: SBRT for oligometastatic disease to the lung using 8-12 Gy daily fractions over five treatments resulted in excellent 1- and 2-year LC rates. Most local failures occurred within the first 12 months, with five local failures associated with colorectal cancer. The treatment is safe using this radiation fractionation schedule with no therapy-related pneumonitis.

Keywords: Stereotactic body radiotherapy (SBRT); lung cancer; oligometastases

Submitted Aug 08, 2013. Accepted for publication Dec 03, 2013.
doi: 10.3978/j.issn.2072-1439.2013.12.03
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2013.12.03

Introduction

Metastases to lungs from various malignancies have generally been regarded as incurable and ultimately fatal (1,2). Systemic chemotherapy has played a major palliative role in keeping cancer-related symptoms and disease progression under control for a limited time, after which these tumors generally become refractory to chemotherapy. Long-term survival with chemotherapy for metastatic lung disease is extremely rare (2). A select group of patients develop lung metastases that are limited in number and extent, and are amenable to surgical or locally ablative techniques such as stereotactic body radiotherapy (SBRT) (2-4). In others with widespread disease, effective chemotherapy with near complete response could result

Table 1 Patient and treatment characteristics

Characteristics	N
Age, 38-81 (median 51) years	
Gender	
Male	17
Female	17
Primary site	
Colorectal	13
Head and neck	6
Breast	4
Melanoma	4
Sarcoma	4
Renal carcinoma	3
Follow-up	
Range, 2.4 to 54 months	
Median FU period, 16.7 months	
Isocenter dose (Gy)	
40	11
45	4
50	18
60	1
Number of lung lesions treated per patient	
N=1	19
N=2	7
N=3	5
N=5	3

in limited lung metastases (2,3). This state of limited metastases was coined "oligometastasis" in the 1990s when radiation planning and delivery were experiencing major technical advances (5). Patients with oligometastasis have been considered candidates for curative treatments because prolonging survival can be expected (6-8).

With the advent of improved 3-dimensional computed tomography (CT) based radiation treatment planning and more precise dose delivery methods, treatments using radiation have taken a leap forward in offering a more curative and less toxic approach in the management of cancers overall. The dose escalation coupled with high doses of radiation delivered per fraction in a short overall treatment time using high degrees of anatomic targeting accuracy results in an improved therapeutic ratio while minimizing radiation-associated early and late pulmonary toxicity. SBRT utilizes a large number of non-opposing beams with anatomic targeting using stereotactic localization and/or image guidance. Improved reproducibility in patient set-up and targeting accuracy facilitates the use of large fraction, ablative radiation doses resulting in high local control (LC) rates.

Many reports are now available on the use of SBRT for oligometastatic lung disease, although patient cohorts in these studies are heterogeneous with respect to cancer types and selection criteria (2-4,9-11). SBRT can either be done for patients with new overt oligometastatic disease (patients not suitable for chemotherapy/surgery), or after the chemotherapy options have been exhausted. Furthermore, the extent of oligometastatic disease varies in patients included in different studies. For example, an early study by the University of Rochester included patients with five or fewer lesions, not necessarily confined to the thorax (2). Kyoto University uses criteria of one or two pulmonary metastases, tumor diameter <4 cm, locally controlled primary tumor, and no other metastatic sites (12). Duke University's criteria are stage IV cancer (any histology) with 1 to 5 metastases, with each metastasis ≤10 cm or ≤500 mL in volume on standard imaging (4).

The University of Rochester started using SBRT for oligometastasis in 2001 and has previously published survival and tumor control data showing 2-4 years overall survival (OS) rates of 50% and 28% and progression-free survival (PFS) rates of 26% and 26% respectively. Most of these patients were treated with a 10-fraction regimen using 4-6 Gy daily. As the outcomes of SBRT with less protracted regimes of five or fewer fractions were published by other institutions, our policy changed from ten-fraction SBRT to five-fraction SBRT using larger daily fraction sizes of 8-12 Gy. The present retrospective study was carried out to analyze the survival and tumor control and failure patterns for oligometastatic lung metastases treated with five fractions of SBRT among patients with chemorefractory disease or who were not candidates for chemotherapy or surgical resection.

Methods

Between January 2008 and December 2011, thirty-four patients with oligometastatic cancer to the lungs who were considered refractory to (n=28) or ineligible for (n=6) chemotherapy were treated with SBRT. The 17 male and 17 female patients' ages ranged from 38 to 81 years with a median age of 51 years (*Table 1*). The study was approved by the University of Rochester Medical Center Research Subjects Review Board.

The inclusion criteria of this study included patients with one to five lung metastases, age >18, KPS >70%, tumor diameter (on CT) <5 cm, locally controlled primary tumor, and no other active metastatic sites. Patients with primary non-small cell lung cancer were not included [as patients with separate nodules within the same lung are defined as T3 (same lobe) to T4 disease (same lung, different lobes)]. The work up included contrast enhanced CT of the thorax and upper abdomen and FDG-PET. Patients were followed with CT or PET-CT every 3-6 months. Patients with no progression of treated lesions who developed new radiographically apparent oligometastatic lesions on follow-up imaging were allowed to undergo repeat cycle(s) of SBRT for new lesions (13).

SBRT technique

The SBRT techniques that have been described in detail in previous publications from our group are briefly summarized here (2). All patients undergoing initial CT simulation required immobilization with a vacuum cushion device. All patients were treated with the Novalis ExacTrac system (BrainLab Inc.). The ExacTrac patient positioning platform using infrared reflecting body fiducial markers monitored by two ceiling mounted infrared cameras was used for patient positioning and real-time monitoring. Respiratory motion was minimized by using relaxed expiratory breath hold techniques (in most patients) or shallow breathing (in patients with poor lung function). Patients also underwent a CT in the set-up position, which was fused to the planning CT, prior to treatment and after the second fraction to ensure three-dimensional set-up accuracy. The gross tumor volume (GTV) was delineated using CT and fused PET imaging when needed. The use of arcs and non co-planner beams was encouraged. Dose volume histograms (DVH) were calculated for the lung (defined as total lung minus GTV), heart, esophagus, spinal cord, and liver. The planning target volume (PTV) was defined as a 7 mm circumferential and 11 mm superior-inferior expansion of the GTV (with no expansion for CTV) (2,3,13). The 80% isodose line encompassed the PTV, with isocenter dose defined as 100% of the prescribed dose. The prescribed target dose was determined based on the DVH of normal (uninvolved) lung and surrounding organs. The median prescription dose was 50 Gy in five fractions (range, 40-60 Gy) to isocenter with 80-100% isodose covering 95% of PTV. Patients were required to have 1,000 mL of tumor free lung, with a volume of lung receiving >20 Gy (V_{20}) less than 25%. The spinal cord maximum was required to be <4.5 Gy/fraction. Care was taken so that hot spots (i.e., >80% isodose) occurred solely within the GTV. The dose for smaller peripheral tumors was mostly 50-60 Gy and the dose for larger central tumors was mostly 40-50 Gy.

Outcomes/statistics

The primary end point was tumor LC and secondary end points included regional control as well as OS. Actuarial tumor control and survival were calculated using the Kaplan-Meier actuarial survival analyses. OS was defined from date of completion of SBRT until death or last follow-up. Patient LC was scored as an event if any treated lesion grew by ≥20%, based on the Response Evaluation Criteria In Solid Tumors (RECIST) criteria or a local failure was confirmed pathologically. LC was analyzed per patient, meaning that if a patient had more than one lesion treated, progression of any of the treated lesions was considered a local failure. LC was analyzed by tumor size; among patients with more than one lesion, treated tumor size represents the largest lesion treated. Among patients who underwent repeat courses of SBRT for new lesions(s), only the LC of the index lesion(s) was considered in this study. STATA version 9.2 was used for all data analysis.

Results

The primary cancer sites among the 34 patients included colorectal (n=13), head and neck (n=6), breast (n=4), melanoma (n=4), sarcoma (n=4) and renal carcinoma (n=3). Follow-up ranged from 2.4 to 54 months (median 16.7 months) (*Table 1*). Nineteen patients had one lesion treated, seven patients had two lesions, five patients had three lesions, and three patients had five lesions treated with SBRT.

The 1-, 2-, and 3-year patient LC rates for all comers were 93%, 88%, and 80% respectively (*Figure 1*) with 1-, 2-, and 3-year OS of 62%, 44%, and 23% respectively. Four patients had lung metastases recur locally within 12 months; only one patient developed a local recurrence beyond 24 months (at 26 months), although only 12 patients were alive with follow-up beyond two years.

Among the 25 patients with maximal lesion size of 1- <2 cm, the 1- and 2-year patient LC rates were 95% and 88%. Among the seven patients with maximal lesion size of 2- <3 cm, the 1- and 2-year patient LC rates were 86% and 86%, and not significantly different than for patients with smaller lesions (*Figure 2*). Only one patient was treated

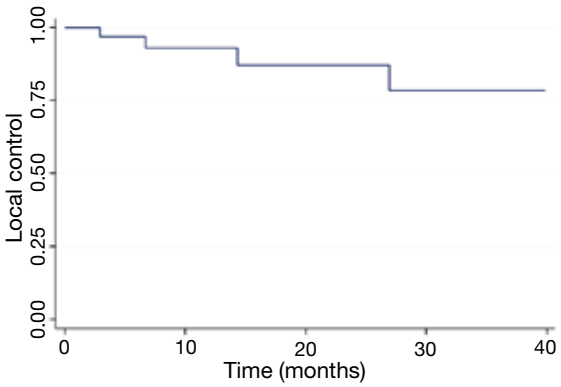


Figure 1 Overall local control among 34 patients.

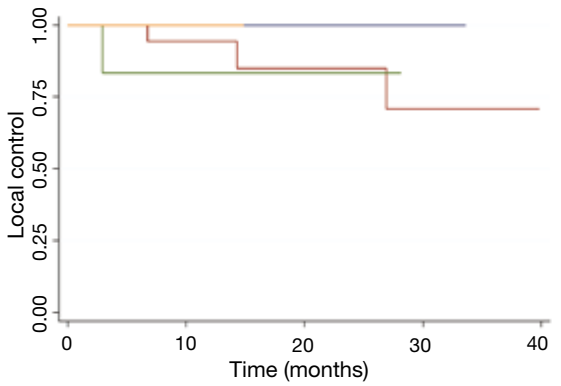


Figure 2 Overall local control based on lesion size at one year and at two years.

with a maximal lesion size of >3 cm and only one patient was treated with a maximal lesion size <1 cm (neither of whom experienced a local recurrence. All five patients with local recurrences had colorectal cancer. Gender (P=0.30), previous treatment with chemotherapy (P=0.95), radiation dose (0.26), and nodule size (P=0.97) were not statistically significant on univariate analysis. A multivariate analysis was not done because of the small number of events. Symptomatic pneumonitis (grade ≥2) was not seen in any patient. Post-radiation fibrotic changes and consolidation occurred in 26 of the 34 patients.

Discussion

Metastatic disease to lung is one of the most common life threatening complications of cancer (2) and has been regarded as an incurable condition (1). However, patients with oligometastatic lung metastases have been considered candidates for curative treatment because of prolonged tumor LC rates and OS. Improved imaging now allows detection of tumor metastases at a smaller size and effective systemic therapy allows for potential 'downstaging' widely metastatic disease to an oligometastatic state, and thus provides an opportunity for local therapy as consolidation for patients with minimal bulk metastases (2). Surgical pulmonary metastatectomy in suitable patients with oligometastases is recognized as a potential curative treatment, and published data reveal a 5-year survival rate in these patients to be 20-40% (14). Alternatively, SBRT has also been used as a curative treatment of oligometastasis especially in patients who are not eligible candidates for surgery, either because of medical comorbidities, or because central lesions and/or multiple lesions would require a more extensive surgery than the patient could tolerate. The International Registry of Lung Metastases (IRLM) (14) reported the results of pulmonary complete resection in a large number of patients with lung metastases showing a 2-, 5-, and 10-year survival rate of 70%, 36%, and 26% respectively. In one of the largest published series on SBRT comprising of 175 patients (311 lesions), Siva *et al.* (15) has shown encouraging results with an OS rate of 54.5%. The IRLM study (14) also reported that a disease-free interval of more than 36 months and single metastasis were good prognostic factors. In our current study, gender (P=0.30), previous treatment with chemotherapy (P=0.95), radiation dose (0.11), and nodule size (P=0.97) were not statistically significant on univariate analysis. Symptomatic pneumonitis requiring treatment or hospitalization was not seen in any of the patients treated with SBRT.

Several reports have been published regarding the outcomes of SBRT for metastatic lung tumors, but no standard treatment regimens have been defined with respect to the optimal dose and fractionation schedules. From published studies, the dose-fractionation of SBRT varies from 40-60 Gy in 3-10 fractions. Our institution had been using 5 Gy ×10 from the inception of SBRT at the University of Rochester in 2001, but we recently changed the dose to 8-12 Gy in five fractions (2). Japanese studies have shown the correlation of dose effect with improved LC rates. With regards to the biologic effective dose, assuming an alpha/beta ratio of ten, (BED_{10}), Hamamoto *et al.* (16) have reported rather poor LC of 25% at two years using 48 Gy in four fractions (105.6 Gy_{10}) where as another report by Norihisa *et al.* (12) showed that LC rate of 43 metastatic lung tumors was 90% at two years with 60 Gy in five fractions (132 Gy_{10}). A recent multi-institutional phase

I/II study by Rusthoven *et al*. (17) reported a 2-year LC of 96% by 48-60 Gy in three fractions (124-180 Gy_{10}) for 63 metastatic lung lesions. Similarly, McCammon *et al*. (18) showed the dose-LC relationship of SBRT for 246 lesions (primary or metastatic) by using a regimen of 54-60 Gy in three fractions (151-180 Gy_{10}) achieving LC of 89% at three years.

Our earlier institutional report (2) showed a LC of 83% with 5 Gy fractions for total doses of 50 to 60 Gy, whereas a subsequent report showed LC of 87% at two and six years (3). In the current study, SBRT was delivered to a median dose of 50 Gy (range, 40-60 Gy) in five fractions with 1- and 2-year LC rates of 93% and 87% for all patients. Local progression occurred in four patients within 12 months and the other 30 patients had excellent LC and remained locally NED to date except one patient with primary colon cancer who failed locally at 26 months.

Onishi *et al*. (19) concluded that BED_{10} of >100 Gy at isocenter is preferable for treatment of primary lung cancer to achieve an optimal OS rate. For SBRT for pulmonary metastases, the BED_{10} of published dose-fractionation schedules ranges from 70-162 Gy, with the 2-year survival ranging from 33% to 84% in various studies (11,12,20,21). Norihisa *et al*. (12) have reported a 2-year survival rate of 84% in their study, whereas Lee *et al*. (11) have reported a 2-year survival rate of 68% from their study. Onimaru *et al*. (20) and Wulf *et al*. (21) reported survival rates of 49% and 33% at two years. The median and OS in present series was 16 months and 62%, 44%, and 23% at one, two, and three years, respectively.

When comparing dose fractionation schemes, it is important to recognize that different institutions prescribe dose differently and use different methodologies to plan and deliver SBRT. The dose can be prescribed to a point (i.e., isocenter), volume (i.e., GTV or PTV), or isodose line. Also, the PTV margins vary from institute to institute depending upon set up accuracy. Furthermore, defining the PTV reflects a difference in CT scanning with regards to free breathing *vs*. breath holding and fast *vs*. slow scan times (12). Also, some utilize 4-D scanning and definition of an ITV. Difference in dose calculation by taking in to account tissue heterogeneity corrections would affect margin dose in lung tumors (12). Lastly, differences in planning approaches (fixed *vs*. arcing beams; 3-D conformal *vs*. IMRT *vs*. VMAT) may also be relevant.

The primary cancer site seems to have a significant effect on outcomes of patients treated with SBRT. Milano *et al*. (22) reported earlier results from our institution using 50 Gy in ten fractions with 2-year LC of all lesions being 77%, concluding that metastatic tumors originating from the pancreas, biliary, liver, or colon were associated with poorer LC. Hamamoto *et al*. (16) also reported LC of 25% at two years and attributed the poor outcome to a large proportion of metastatic tumors from the colon (67%). Similarly Kim *et al*. (23) have also reported a poor outcome with 3-year LC of 52.7% using 39-51 Gy in three fractions. Takeda *et al*. (24) compared outcomes of primary lung tumors with metastases treated by SBRT showing a LC of 94% *vs*. 72% at two years (P<0.05). The present study also showed poor outcome with colorectal cancers, as all of the local failures were seen in this group.

In many studies, tumor size plays a significant role in predicting the LC, as various studies have shown a trend for improved LC with smaller size of the tumor and interval tumor volume (ITV <17 mL, i.e., approximately 3 cm in diameter) (23). A study by McCammon *et al*. (18) showed better LC in smaller tumors with GTV <8.9 mL (P=0.003). Kim *et al*. (25) reported that tumors <2.5 cm were associated with higher LC than tumors >2.5 cm; 100% *vs*. 82.3% in patients with primary or metastases lung tumors. Oh *et al*. (1) also reported that tumors <2.5 cm have better LC 98.3% *vs*. 77.8% (P<0.01). Our current study did not show a statistically significant effect of tumor size on patient LC, albeit with a relatively narrow range of size for most patients and a heterogeneous patient population.

Weaknesses of our study include the small retrospective nature, with a diverse population, in terms of primary site and histology. Because the majority of patients were treated with the same dose (50 Gy in five fractions), and the dose range was not large, we could not adequately analyze a dose-response relationship. Nevertheless, we are able to report promising LC and survival outcomes in this cohort of patients with oligmetastatic disease of the lung. Our conclusion is that SBRT for oligometastatic cancer to the lungs is effective and well tolerated for nonsurgical/chemorefractory patients.

Acknowledgements

The authors thank Ms. Laura Finger for editorial assistance. *Disclosure:* The authors declare no sources of funding or conflicts of interest.

References

1. Oh D, Ahn YC, Seo JM, et al. Potentially curative

stereotactic body radiation therapy (SBRT) for single or oligometastais to the lung. Acta Oncol 2012;51:596-602.
2. Okunieff P, Petersen AL, Philip A, et al. Stereotactic Body Radiation Therapy (SBRT) for lung metastases. Acta Oncol 2006;45:808-17.
3. Milano MT, Katz AW, Zhang H, et al. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. Int J Radiat Oncol Biol Phys 2012;83:878-86.
4. Salama JK, Hasselle MD, Chmura SJ, et al. Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. Cancer 2012;118:2962-70.
5. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13:8-10.
6. Singh D, Yi WS, Brasacchio RA, et al. Is there a favorable subset of patients with prostate cancer who develop oligometastases? Int J Radiat Oncol Biol Phys 2004;58:3-10.
7. Kavanagh BD, McGarry RC, Timmerman RD. Extracranial radiosurgery (stereotactic body radiation therapy) for oligometastases. Semin Radiat Oncol 2006;16:77-84.
8. Yang JC, Abad J, Sherry R. Treatment of oligometastases after successful immunotherapy. Semin Radiat Oncol 2006;16:131-5.
9. Nagata Y, Negoro Y, Aoki T, et al. Clinical outcomes of 3D conformal hypofractionated single high-dose radiotherapy for one or two lung tumors using a stereotactic body frame. Int J Radiat Oncol Biol Phys 2002;52:1041-6.
10. Hof H, Herfarth KK, Münter M, et al. Stereotactic single-dose radiotherapy of stage I non-small-cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 2003;56:335-41.
11. Lee SW, Choi EK, Park HJ, et al. Stereotactic body frame based fractionated radiosurgery on consecutive days for primary or metastatic tumors in the lung. Lung Cancer 2003;40:309-15.
12. Norihisa Y, Nagata Y, Takayama K, et al. Stereotactic body radiotherapy for oligometastatic lung tumors. Int J Radiat Oncol Biol Phys 2008;72:398-403.
13. Milano MT, Philip A, Okunieff P. Analysis of patients with oligometastases undergoing two or more curative-intent stereotactic radiotherapy courses. Int J Radiat Oncol Biol Phys 2009;73:832-7.
14. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. The International Registry of Lung Metastases. J Thorac Cardiovasc Surg 1997;113:37-49.
15. Siva S, MacManus M, Ball D. Stereotactic radiotherapy for pulmonary oligometastases: a systematic review. J Thorac Oncol 2010;5:1091-9.
16. Hamamoto Y, Kataoka M, Yamashita M, et al. Local control of metastatic lung tumors treated with SBRT of 48 Gy in four fractions: in comparison with primary lung cancer. Jpn J Clin Oncol 2010;40:125-9.
17. Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol 2009;27:1579-84.
18. McCammon R, Schefter TE, Gaspar LE, et al. Observation of a dose-control relationship for lung and liver tumors after stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2009;73:112-8.
19. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004;101:1623-31.
20. Onimaru R, Shirato H, Shimizu S, et al. Tolerance of organs at risk in small-volume, hypofractionated, image-guided radiotherapy for primary and metastatic lung cancers. Int J Radiat Oncol Biol Phys 2003;56:126-35.
21. Wulf J, Haedinger U, Oppitz U, et al. Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: a noninvasive treatment approach in medically inoperable patients. Int J Radiat Oncol Biol Phys 2004;60:186-96.
22. Milano MT, Katz AW, Schell MC, et al. Descriptive analysis of oligometastatic lesions treated with curative-intent stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2008;72:1516-22.
23. Kim MS, Yoo SY, Cho CK, et al. Stereotactic body radiation therapy using three fractions for isolated lung recurrence from colorectal cancer. Oncology 2009;76:212-9.
24. Takeda A, Kunieda E, Ohashi T, et al. Stereotactic body radiotherapy (SBRT) for oligometastatic lung tumors from colorectal cancer and other primary cancers in comparison with primary lung cancer. Radiother Oncol 2011;101:255-9.
25. Kim H, Ahn YC, Park HC, et al. Results and prognostic factors of hypofractionated stereotactic radiation therapy for primary or metastatic lung cancer. J Thorac Oncol 2010;5:526-32.

Cite this article as: Singh D, Chen Y, Hare MZ, Usuki KY, Zhang H, Lundquist T, Joyce N, Schell MC, Milano MT. Local control rates with five-fraction stereotactic body radiotherapy for oligometastatic cancer to the lung. J Thorac Dis 2014;6(4):369-374. doi: 10.3978/j.issn.2072-1439.2013.12.03

Current Evidence

Is staging mediastinoscopy necessary before stereotactic body radiotherapy for inoperable early stage lung cancer?

Jean-Claude M. Rwigema, Percy Lee

Department of Radiation Oncology, University of California, Los Angeles, CA 90095, USA
Correspondence to: Percy Lee, MD. The 200 UCLA Medical Plaza, B265, Los Angeles, CA 90095, USA. Email: PercyLee@mednet.ucla.edu.

Submitted Nov 20, 2015. Accepted for publication Dec 06, 2015.
doi: 10.3978/j.issn.2072-1439.2015.12.54
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.12.54

Patients with stage I non-small lung cancer (NSCLC) who are managed with stereotactic body radiotherapy (SBRT) do not routinely undergo mediastinal lymph node sampling, although a significant proportion of these patients can harbor metastatic subclinical mediastinal disease. For instance, results of a retrospective analysis by Sarwate *et al*., in which 59 patients with medically inoperable NSCLC, had pathologic mediastinal staging prior to SBRT consideration, indicated that 16% of patients had positive mediastinal disease, which prompted alternative treatment options (1).

Nevertheless, in addition to excellent primary tumor control and overall survival rates that are comparable to historical data of patients who undergo lobectomy, the incidence of mediastinum disease recurrence rates in patients treated with SBRT without pathological staging appear to be limited in currently available data (2). Baumann *et al*. reported only 5% regional nodal recurrence rate with a median follow-up of 35 months, in a prospective phase II trial of 57 patients with medically inoperable stage I NSCLC treated with SBRT (3). Similarly, in RTOG 0236, a phase II trial of 55 patients with medically inoperable disease, Timmerman *et al*. reported a 3.6% mediastinal failure rate with a median follow-up of 34.4 months (4). However, in their recent update with long-term follow-up, Timmerman *et al*. noted an increased 5-year loco-regional failure rate at 38%, while the 5-year primary tumor control remained high at 93%, and without increased late toxicity (5). Data from retrospective series have also shown low mediastinum failure rates with limited follow-up. Senthi *et al*. reported outcomes of a series of 676 patients with T12N0M0 treated with SBRT, where they obtained a 6.4% overall regional recurrence rate with a median follow-up of 32.9 months (6). In our single institutional retrospective analysis of 46 patients with stage I NSCLC treated with SBRT, we achieved a 4.9% regional (i.e., ipsilateral and contralateral mediastinum plus supraclavicular node regions) nodal recurrence rate at a median follow-up of 16.8 months (7).

Emerging data suggest no differences in outcomes regardless of whether or not surgical staging is performed before SBRT. Fischer-Valuck *et al*. analyzed outcomes of 88 patients with early stage NSCLC, in whom 73.9% had biopsy-proven disease compared to radiographic only diagnosis in the remaining group (8). They found no differences in 3-year local progression-free survival, regional lymph node metastasis-free survival and overall survival rates between the two groups (8). Another recent study from Yale University demonstrated that loco-regional recurrence free-survival and overall survival were similar in 286 patients treated with SBRT with or without mediastinal staging with a median follow-up of 20.3 months (9).

In the article by Paravati *et al*., they evaluated the negative predictive value (NPV) of PETCT for nodal disease in 144 patients with clinically node negative stage I NSCLC who underwent surgical resection at single institution (10). Of the 144 patients, 19 patients were upstaged due to the presence of nodal metastases resulting in an overall nodal NPV of 87%. On multivariate analysis they noted that larger tumor size, age at surgery and central tumor location were significant predictors of occult nodal metastasis (10). Of note, they defined central tumors as those within the inner third of lung parenchyma, unlike RTOG 0236 criteria, that defines central tumors as those within 2 cm of the bronchial tree, major vessels, esophagus, heart, trachea, pericardium, or vertebral body (4). Data

from other surgical series suggest potentially significant rates of occult nodal metastases after pathologic mediastinal staging of patients with stage I NSCLC. In a series by Robson *et al*. (11), of 128 patients with stage I NSCLC who underwent surgery, they found an 8.9% incidence of hilar/mediastinal occult metastatic disease in peripheral tumors compared to 33.3% for central tumors (defined as per RTOG criteria).

Surgical series report mediastinum failure rates that are comparable to SBRT data but with longer follow-up. A retrospective analysis by Asamura *et al*., of 337 patients with peripheral stage I (94.7% T1) NSCLC who underwent lobectomy (97%) or pneumonectomy (3%) with lymphadenectomy, of whom 305 patients had clinical N0 status, 68 (22.3%) were found to have mediastinal and hilar LN involvement after mediastinoscopy (12). With a follow-up of at least 5 years, there was a 5.3% (1 of 213) incidence of mediastinal recurrence. Trodella *et al*. reported results of a phase III trial comparing postoperative radiotherapy to surgery alone in 104 patients with stage I NSCLC who underwent at least a lobectomy with lymphadenectomy (13). In the surgery alone arm there was a 9.4% mediastinal recurrence rate with a mean follow-up of 63 months. An analysis of patterns of recurrence of patients with resected stage I NSCLC from a multicenter Lung Cancer Study Group trial and showed a 7% mediastinal recurrence with a mean follow-up of 41 months (14).

One could expect higher regional relapse rates in surgical series than observed, if preoperative mediastinal lymph node sampling were omitted, simply based on the potentially significant rates of occult nodal metastases that can be discovered prior to surgery. On the other hand, it is also possible that the low mediastinum relapse rates noted in most SBRT series may be due to shorter follow-up than in surgical series, such that occult disease may take a long time to manifest clinically. Moreover, some SBRT series report results of patients treated without biopsy confirmation of cancer, which would artificially lower the incidence of mediastinum recurrence if benign lesions are inadvertently included (15).

So when does it make sense to subject patients to an invasive staging mediastinoscopy in patients with inoperable stage I NSCLC? It seems reasonable for patients with larger tumors and centrally-located tumors to undergo routine mediastinoscopy, as suggested by Paravati *et al*. and others, since there is an increased risk of subclinical nodal disease [mainly N2 (13)], as this can alter treatment recommendations (10,16,17). However, can we still be on par with surgery while avoiding a mediastinoscopy in low-risk inoperable patients (i.e., small peripheral tumors)? We propose that in patients with borderline resectable disease, it can be useful to advocate for a pathologic lymph node sampling procedure as the reported high NPV, PETCT can still under-stage up to 32% of patients with stage I NSCLC (18). Yet, the low regional nodal relapse rates observed after SBRT with PETCT staging only, are somewhat are paradoxical and may not be fully explained by inadequate follow-up with SBRT. Given that incidental SBRT dose to the mediastinum while treating stage I NSCLC is too low (i.e., <5 Gy) to account for subclinical nodal disease clearance, alternative mechanisms that are increasingly supported by emerging data proposing immune-mediated effects of SBRT outside the primary target, may play a role (7,19,20). However, further studies are warranted to further elucidate the impact of abscopal effects of ablative radiotherapy on overall disease control in early stage NSCLC.

In summary, in patients with inoperable disease who may not live long enough to develop regional recurrences, we should not change our practice to recommend an invasive staging procedure before SBRT without clearly defined evidence-based guidelines from prospective randomized data.

Acknowledgements

None.

Footnote

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

References

1. Sarwate D, Sarkar S, Krimsky WS, et al. Optimization of mediastinal staging in potential candidates for stereotactic radiosurgery of the chest. J Thorac Cardiovasc Surg 2012;144:81-6.
2. Stephans K. Stereotactic body radiotherapy for stage I non-small cell lung cancer. Cleve Clin J Med 2012;79 Electronic Suppl 1:eS26-31.
3. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.

4. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
5. Timmerman RD, Hu C, Michalski J, et al. Long-term Results of RTOG 0236: A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2014;1:S30.
6. Senthi S, Lagerwaard FJ, Haasbeek CJ, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol 2012;13:802-9.
7. Rwigema JC, Chen AM, Wang PC, et al. Incidental mediastinal dose does not explain low mediastinal node recurrence rates in patients with early-stage NSCLC treated with stereotactic body radiotherapy. Clin Lung Cancer 2014;15:287-93.
8. Fischer-Valuck BW, Boggs H, Katz S, et al. Comparison of stereotactic body radiation therapy for biopsy-proven versus radiographically diagnosed early-stage non-small lung cancer: a single-institution experience. Tumori 2015;101:287-93.
9. Corso CD, Lloyd S, Harder E, et al. Invasive Mediastinal Staging Does Not Improve Outcomes Over PET Alone in Early-Stage NSCLC Treated with SBRT. Int J Radiat Oncol Biol Phys 2014; 90:S216-7.
10. Paravati AJ, Johnstone DW, Seltzer MA, et al. Negative predictive value (NPV) of FDG PET-CT for nodal disease in clinically node-negative early stage lung cancer (AJCC 7th ed T1-2aN0) and identification of risk factors for occult nodal (pN1-N2) metastasis: implications for SBRT. Transl Cancer Res 2014;3:313-9.
11. Robson JM, Vaidyanathan S, Cheyne L, et al. Occult nodal disease in patients with non-small-cell lung cancer who are suitable for stereotactic ablative body radiation. Clin Lung Cancer 2014;15:466-9.
12. Asamura H, Nakayama H, Kondo H, et al. Lymph node involvement, recurrence, and prognosis in resected small, peripheral, non-small-cell lung carcinomas: are these carcinomas candidates for video-assisted lobectomy? J Thorac Cardiovasc Surg 1996;111:1125-34.
13. Trodella L, Granone P, Valente S, et al. Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. Radiother Oncol 2002;62:11-9.
14. Feld R, Rubinstein LV, Weisenberger TH. Sites of recurrence in resected stage I non-small-cell lung cancer: a guide for future studies. J Clin Oncol 1984;2:1352-8.
15. Takeda A, Kunieda E, Sanuki N, et al. Stereotactic body radiotherapy (SBRT) for solitary pulmonary nodules clinically diagnosed as lung cancer with no pathological confirmation: comparison with non-small-cell lung cancer. Lung Cancer 2012;77:77-82.
16. Wang J, Welch K, Wang L, et al. Negative predictive value of positron emission tomography and computed tomography for stage T1-2N0 non-small-cell lung cancer: a meta-analysis. Clin Lung Cancer 2012;13:81-9.
17. Al-Sarraf N, Aziz R, Gately K, et al. Pattern and predictors of occult mediastinal lymph node involvement in non-small cell lung cancer patients with negative mediastinal uptake on positron emission tomography. Eur J Cardiothorac Surg 2008;33:104-9.
18. Cerfolio RJ, Bryant AS. Survival of patients with true pathologic stage I non-small cell lung cancer. Ann Thorac Surg 2009;88:917-22; discussion 922-3.
19. Lee Y, Auh SL, Wang Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood 2009;114:589-95.
20. Formenti SC, Demaria S. Systemic effects of local radiotherapy. Lancet Oncol 2009;10:718-26.

Cite this article as: Rwigema JC, Lee P. Is staging mediastinoscopy necessary before stereotactic body radiotherapy for inoperable early stage lung cancer? J Thorac Dis 2015;7(12):E612-E614. doi: 10.3978/j.issn.2072-1439.2015.12.54

Current Evidence

A millimeter miss is as good as a thousand miles: The role of accurate target localization in lung stereotactic body radiation therapy

Allan Y. Chen[1], Michelle B. Chen[2], Yi-Jen Chen[2]

[1]Department of Radiation Oncology, The Permanente Medical Group, Sacramento, CA, USA; [2]Radiation Oncology, City of Hope Medical Center, Duarte, CA, USA

Correspondence to: Allan Y. Chen, MD, PhD. Department of Radiation Oncology, The Permanente Medical Group, Sacramento, CA, USA. Email: allan.y.chen@kp.org.

Submitted Mar 08, 2012. Accepted for publication Mar 15, 2012.
doi: 10.3978/j.issn.2072-1439.2012.03.12
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2012.03.12

Surgical intervention with lobectomy and mediastinal lymph node dissection is considered the treatment of choice in early stage non-small cell lung cancer (NSCLC) (1). However, approximately 20-25% of patients with early stage NSCLC are poor surgical candidates for lobectomy because of concomitant severe cardiac or pulmonary co-morbidities. For these patients, conventional radiotherapy with 60 to 70 Gy delivered in 30-35 fractions over a 6-7-week period generally resulted in poor 20-40% 3-year and 10-30% 5-year survival rates (2,3). This inadequate tumor control is mainly due to the insufficient tumor dose that is limited by normal tissue toxicity and possible target-miss caused by tumor mobility.

Stereotactic body radiation therapy (SBRT), or stereotactic ablative radiotherapy (SABR), has been emerging as an excellent alternative for medically inoperable early stage NSCLC patients. Conceptually derived from cranial stereotactic radiosurgery, the planning and delivery of SBRT is characterized by highly target-conformal dose distributions with steep dose gradients towards normal tissues, allowing the administration of potent tumor-ablative radiation doses. In lung SBRT, a total of 45-50 Gy of radiation is delivered in 3-5 fractions over a 10-20 days' duration. Calculated by LQ with α/β=10 Gy, a less than 5 cm tumor is generally treated with higher than 100 biologically equivalent dose (BED). Available data demonstrated an impressive 80-95% local tumor control at 2-5 years and good lung function preservation (3-6). The recently published RTOG 0236 phase II study demonstrated 3-years 98% local tumor control and 56% survival (7). This result is quite comparable to the reported 53% 5-year survival with surgical resection, based on thousands of patients in the International Association for the Study of Lung Cancer Staging Project (8). Lung SBRT is comparably superior than radiofrequency ablation (RFA), an alternative invasive procedure with a moderate 60% tumor control rate for less than 3 cm tumors, but is also associated with much higher procedure-related morbidities, mainly caused by pneumothorax and hemorrhage (9).

How to accurately locate small pulmonary targets for lung SBRT is the subject of one article published in this issue of Journal of Thoracic Disease. In their study, Shen *et al*. investigated the application of double CT imaging to measure the respiratory movement of small pulmonary tumors during SBRT (10). A total of 122 small pulmonary tumors in 45 patients were measured. Four-slice spiral CT scans were conducted twice in all patients- once each at the end of quiet inhalation and of exhalation, and three times in 17 patients—with one additional free breathing image. The displacement of the tumor center in three directions was measured. The study showed an overall 3D motion of 10.10±7.16 mm in 122 tumors, with 1.96±2.03, 5.19±4.69 and 7.38±6.48 mm in the X, Y and Z directions, respectively. The extent of tumor motion was influenced by the pulmonary location of individual tumor: greater motion was noted in tumors in the lower, left and anterior locations than in the upper, right and posterior locations. In contrast to 4-dimentional CT, this is a relatively less expansive, yet practical method for target localization. Their conclusions are in general agreement with published results (11).

The success of lung SBRT relies largely on accurate target localization, which enables precise ablative

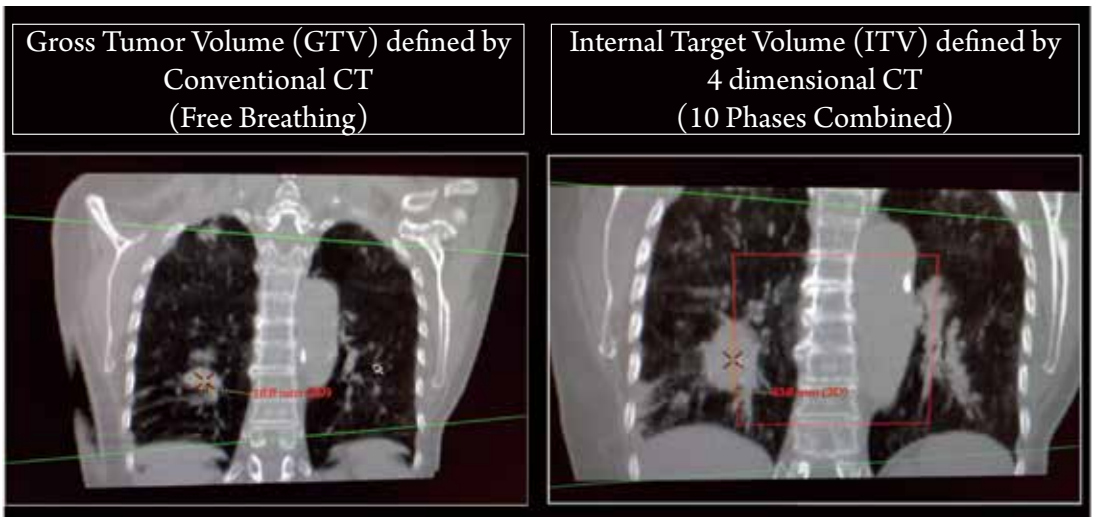


Figure 1 Four-dimensional CT (4D-CT) reduces motion artifact and allows accurate determination of internal target volume (ITV) for small-sized pulmonary tumors.

radiotherapy to target while maximizing the spared surrounding normal tissues from treatment-related side effects. It is an eminent observation that small-sized lung tumors are moving targets, which changes not only their locations, but also their shapes and volumes as the lung inflates and deflates. In addition, respiratory-induced motion can cause severe geometrical distortion of tumors and normal tissues in free breathing CT scanning. A variety of methods and techniques have been used to determine the exact location of a moving target inside of lung. Voluntary breath-holding during imaging and treatment represents one simple, but often problematic approach in many lung cancer patients due to poor lung function and anxiety issues. Four-dimensional CT (4D-CT) is currently considered a standard methodology to reduce motion artifact and allow accurate determination of internal target volume (ITV; *Figure 1*). In 4D-CT, an over-sampled spiral CT scan with continuous slices is acquired simultaneously, while the respiratory motion (arbitrarily divided into 10 phases) is recorded by an infrared camera-based motion-tracking system (12). 4D-CT is capable of accurately defining the location and volume of the tumor and its surrounding organs over time during breathing cycles.

A famous Chinese idiom - “A Millimeter Miss is as Good as a Thousand Miles” applies to how in medicine, even slightly subtle errors may lead to huge consequences. Target localization for lung SBRT represents one such situation, in which inaccuracy in millimeters may result in the dire consequence of treatment failure.

References

1. Wright G, Manser RL, Byrnes G, Hart D, Campbell DA. Surgery for non-small cell lung cancer: systematic review and meta-analysis of randomised controlled trials. Thorax 2006;61:597-603.
2. Sibley GS, Jamieson TA, Marks LB, Anscher MS, Prosnitz LR. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. Int J Radiat Oncol Biol Phys 1998;40:149-54.
3. Cheung PC, Mackillop WJ, Dixon P, Brundage MD, Youssef YM, Zhou S. Involved-field radiotherapy alone for early-stage non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2000;48:703-10.
4. Henderson M, McGarry R, Yiannoutsos C, Fakiris A, Hoopes D, Williams M, et al. Baseline pulmonary function as a predictor for survival and decline in pulmonary function over time in patients undergoing stereotactic body radiotherapy for the treatment of stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;72:404-9.
5. Kavanagh, B. D. & Timmerman, R. D., (eds.). "Stereotactic Body Radiation Therapy". Lippincott Williams Wilkins: Philadelphia, 2005.
6. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100.

7. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
8. Rusch VW, Crowley J, Giroux DJ, Goldstraw P, Im JG, Tsuboi M, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol 2007;2:603-12.
9. Haasbeek CJ, Senan S, Smit EF, Paul MA, Slotman BJ, Lagerwaard FJ. Critical review of nonsurgical treatment options for stage I non-small cell lung cancer. Oncologist 2008;13:309-19.
10. Shen G, Wang YJ, Sheng HG, Duan XP, Wang JL, Zhang WJ, et al. Double CT imaging can measure the respiratory movement of small pulmonary tumors during stereotactic ablative radiotherapy. J Thorac Dis 2012;4:131-40.
11. "Image-Guided Radiotherapy of Lung Cancer", Cox, J. D., Chang J. Y. & Komaki R., (ed.), informa, Health care Communications, 2007. Available online: http://informahealthcare.com/doi/pdf/10.3109/9780849387821
12. Vedam SS, Keall PJ, Kini VR, Mostafavi H, Shukla HP, Mohan R. Acquiring a four-dimensional computed tomography dataset using an external respiratory signal. Phys Med Biol 2003;48:45-62.

Cite this article as: Chen AY, Chen MB, Chen YJ. A millimeter miss is as good as a thousand miles: The role of accurate target localization in lung stereotactic body radiation therapy. J Thorac Dis 2012;4(2):109-111. doi: 10.3978/j.issn.2072-1439.2012.03.12

Lung stereotactic body radiotherapy (SBRT): a single institution's outcomes and methodology in the context of a literature review

Erin F. Gillespie, Todd F. Atwood, Ajay P. Sandhu

University of California San Diego, 3855 Health Sciences Drive #0843, La Jolla, CA 92093, USA

Contributions: (I) Conception and design: AP Sandhu; (II) Administrative support: EF Gillespie; (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.

Correspondence to: Ajay P. Sandhu. University of California San Diego, 3822 Health Sciences Drive #0843, La Jolla, CA 92093, USA. Email: apsandhu@ucsd.edu.

Abstract: Lung cancer is the leading cause of cancer death in the United States and worldwide, with the incidence of early stage lung cancer anticipated to rise with increasing use of screening CT. Improvements in systemic therapy have increased the need for durable local control both in primary lung cancer as well as oligometastatic disease to the lung. Since 2007, the University of California San Diego (UCSD) has employed SBRT in the treatment of early stage primary non-small cell histology (NSCLC), intrapulmonary oligometastases, and multiple primary lung cancers (MPLCs) with high efficacy and low toxicity using a frameless technique that involves non-invasive image guidance. We review our center's general approach to management including our experience with clinical outcomes and toxicity in the context of a review of the literature, details of our preferred technique (including simulation and real-time tumor tracking), as well as our results and strategy for patient follow-up using PET to monitor tumor response in the post-SBRT setting.

Keywords: Lung cancer; lung metastases; stereotactic body radiotherapy (SBRT); stereotactic ablative radiotherapy (SABR); stereotactic radiotherapy; motion management

Submitted Aug 14, 2015. Accepted for publication Aug 14, 2015.
doi: 10.3978/j.issn.2218-676X.2015.08.07
View this article at: http://dx.doi.org/10.3978/j.issn.2218-676X.2015.08.07

Background

Lung cancer is the leading cause of cancer death in the United States and worldwide, representing 13-14% of new cancers but 26-28% of deaths from cancer in the US in 2015 (1). Approximately 75% of lung cancer is non-small cell histology (NSCLC), of which up to 25% of patients present with early stage disease. Despite lung cancer afflicting mostly elderly patients, stage I-II NSCLC still portends as little as 5-10% overall survival (OS) at 5 years, compared to 50-80% 5-year OS with therapy. The standard of care for early stage lung cancer has historically been surgical resection due to a randomized clinical trial from the 1960s in which surgery improved OS compared to radiotherapy (RT) (2). RT has since then been reserved for patients who are medically inoperable or decline an invasive procedure, which is usually due to risk of complications. Primary RT in this setting using 3-dimensional conformal techniques (3D-CRT) has continued to show suboptimal results, with 3-year local control of 30-50% and 5-year OS of 15-30% (3-6), largely because dose escalation in conventionally fractionated RT is limited by surrounding normal tissue toxicity.

Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), was first applied extracranially at Indiana University in 2000 (7). By immobilizing the patient in a body frame, the margin required to account for tumor motion and patient setup error could be decreased, therefore enabling dose escalation to a highly conformal target. The RTOG undertook a phase II study in which medically inoperable patients with stage I NSCLC were treated with SBRT and showed 3-year OS of 55% and local

control over 90%, a significant improvement on outcomes with 3D-CRT (8). Other groups have reported comparable results (9), and subsequent analyses showed that achieving a biologically effective dose using an α/β ratio of 10 Gy (BED_{10}) >100 Gy optimized tumor control (10). Further developments in imaging have enabled real-time tumor tracking to further reduce treatment target volume. A recent pooled analysis of two randomized clinical trials of SBRT compared to lobectomy for stage I (<4 cm) NSCLC found that SBRT was at least as effective as surgery, with 3-year OS of 95% (11).

Meanwhile, data has emerged suggesting that treatment of oligometastatic disease to the lung could improve patient outcomes. In the early 1990s, the International Registry of Lung Metastases collected data on 5,206 patients treated with lung metastasectomy in major thoracic centers in both Europe and the United States over the prior four decades, and reported 5-year OS of 36% in patients achieving complete resection (12). With subsequent improvements in systemic therapy coupled with increased efficacy and safety of lung RT as a non-invasive alternative to surgery, lung SBRT has recently been applied in the setting of limited intrapulmonary metastases, with initial publication of phase I/II studies showing efficacy (13).

In January 2007, the University of California San Diego's (UCSD) Department of Radiation Oncology implemented a frameless image-guided lung SBRT program for the treatment of both primary NSCLC and oligometastatic intrapulmonary disease. In this article we will review (I) our center's general approach to management including our experience with clinical outcomes and toxicity in the context of a review of the literature; (II) our preferred technique (including simulation and real-time tumor tracking); as well as (III) our results and strategy for patient follow-up using PET to monitor tumor response in the post-SBRT setting.

General approach to management

Our practice at UCSD has been to offer SBRT for patients with early stage primary NSCLC that are medically inoperable or who refuse surgical resection. The vast majority of these patients have stage I tumors (T1-T2aN0M0) that are biopsy-proven and PET-negative for nodal involvement, though we have also treated many patients with multiple primary lung cancers (MPLCs) (see *Table 1* for summary of published results). While most patients have disease in the lung periphery, up to 30% of patients have central lesions. This reflects the histology of tumors in our patient population, such that the majority (60-70%) of NSCLCs are adenocarcinomas and the minority are squamous cell carcinomas. We also have routinely treated patients with oligometastatic disease to the lung, though these lesions are more often peripheral (over 90%) to minimize the risk of toxicity (21). Our typical RT dose and fractionation is 48 Gy in 4 fractions, with larger and/or central lesions receiving a lower dose of 50 Gy in 5 fractions to reduce possible risk of complications while still achieving BED_{10} of 100 Gy (see *Table 2* for fractionation regimens and BED) as has previously been shown to improve tumor control in the setting of primary NSCLC (10,22). Our dose for oligometastatic lesions has historically been more conservative at 50 Gy in 5 fractions, though we are recently moving toward dose escalation in an attempt to improve local control in the absence of evidence showing increased toxicity. Most recently we have treated elderly patients with very small (T1a, ≤2 cm) peripheral lesions to 30-34 Gy in a single fraction per recent publications showing safety and efficacy from the Cleveland Clinic (23), though our data are not yet published. Patients were followed with clinical exam and imaging (usually chest CT) every 2-6 months. If there was concern on CT image for growth of the lesion, a PET was performed. Local tumor control was defined by biopsy confirming viable tumor or radiographic evidence of increasing size of lesion on follow-up imaging, FDG uptake on PET (if available), and tumor board consensus.

Clinical outcomes and toxicity

Primary non-small cell lung cancer (NSCLC)

For primary NSCLC with mean follow-up of 17-28 months, UCSD has reported 2-year actuarial local control of 91-100% and 2-year OS of 54-74% (14-16). Our studies included primarily T1-T2 lesions, though one patient with T3N0 was included (16). Larger tumor size was associated with inferior rates of distant control (14,16), which is similar to findings from other studies (8,9). We did not, however, find a difference in local control based on tumor size, though this may be due to our small median tumor size (<3 cm) (14). Larger series with greater numbers of tumors >3 cm have shown that larger tumor size (as well as T stage) is associated with decreased local control (8,24). At UCSD, we have employed our technique using 48 Gy in 4 fractions or 50 Gy in 5 fractions in several patients with tumors measuring >5 cm, and our anecdotal experience is that local control rates are lower when compared to smaller lesions treated to similar doses. Increased incidence of local

Table 1 Summary of prior UCSD publications of clinical outcomes, toxicity, and methodology for lung SBRT

Pub	Year	No. of Pts	No. of lesions	Median age	Primary or oligomet	Tumor stage	Median tumor size, mm (range)	Tumor location in lung	SBRT dose/No. of fractions	Median follow-up	Tumor control	Overall survival (2-year or median)	Toxicity
(14)	2007-2009	48	50	79	Primary	T1 (62%) T2 (38%)	22 [10-72]	Central (28%), peripheral (72%)	48 Gy/4	17 mon	2-yr LC 95%; 2-yr NC 91%; 2-yr DC 66%	2-yr OS 54%	12% gr 2 (acute); 2% gr 3 (acute); 0% grade ≥4
(15)	2007-2011	24	24	85	Primary	T1 (79%) T2 (21%)	22 [11-49]	Central (4%), peripheral (96%)	48-56/4-5	28 mon	2-yr LC 100%; 2-yr NC 91%; 2-yr DC 83%	2-yr OS 74%	0% gr ≥3 (acute/chronic)
(16)	2007-2012	55	33 path-confirmed	78	Primary	T1 (57%), T2 (39%), T3 (3%)	27 [10-57]	Central (27%), peripheral (73%)	48-56 Gy/4-5	26 mon	2-yr LC 94%	2-yr OS 64%	13% gr 1-3 (acute); 19% gr 1-2 (chronic)
			24 not biopsied	78		T1 (75%), T2 (21%), T3 (4%)	25 [10-51]	Central (29%), peripheral (71%)	48-52 Gy/4-5	24 mon	2-yr LC 91%	2-yr OS 65%	8.7% gr 1-2 (acute); 13% gr 1-2 (chronic)
(17)	2007-2009	70	50 primary	77	Both	T1 (62%) T2 (38%)	N/A	Lower lobe (23%), middle/upper lobe (77%)	40-52 Gy/3-5	17 mon	2-yr LC 95%	31 mon	0% gr ≥4 (acute/chronic)
			35 mets			N/A	19 [3-72]				2-yr LC 74%	30 mon	
(18)	2007-2009	21	33	61	Oligomet	N/A	15 [3-46]	Central (34%), peripheral (66%)	40-50 Gy/3-5	20 mon	2-yr LC 76%; 2-yr DC 38%	2-yr OS 78%	14% gr 2 (chronic); 0% gr ≥3
(19)	2007-2009	38	22 primary	71	Both	N/A	25	Central (30%), peripheral (70%)	40-52 Gy/3-5	17 mon	2-yr LC 95%	2-yr OS 74%	11% gr 1-2 (acute); 13% gr 1-2 (chronic)
			25 mets			N/A	16				2-yr LC 64%	2-yr OS 84%	
(20)	2007-2011	18	36 (prior SBRT 27)	75	MPLC	T1 (63%), T2 (33%), T3 (4%)	27	Central (26%), peripheral (74%)	48-56 Gy/4-13	20 mon	1.6-yr LC 81%	2-yr OS 62%	0% gr ≥2 (acute); 17% gr 2 (chronic)

UCSD, University of California San Diego's; SBRT, stereotactic body radiotherapy; Pub, publication by article reference number; No. of Pts, number of patients; mon, months; MPLC, multiple primary lung cancer; LC, local control; NC, nodal control; DC, distant control; gr, grade (per CTCAE).

Table 2 BED for various SBRT dose fractionation regimens (α/β =10)

Total dose (Gy)	No. of fractions	BED_{10} (Gy)
54	3	151
34	1	150
30	1	120
48	4	106
60	8	105
50	5	100

BED, biologically effective dose; SBRT, stereotactic body radiotherapy.

recurrence in larger lesions is not unique to SBRT, but is also reported after surgical resection even in the setting of negative margins (12). Therefore, whether this higher failure rate is strictly due to insufficient radiation dose or also pathologic factors associated with larger lesions including satellite tumor cells or microscopic tumor spread is unclear (25).

Histologic subtype of NSCLC in early stage lung cancer appears to affect distant control, with RTOG 0236 prospectively showing 3-year disseminated recurrence in 5.9% of squamous cell carcinomas compared to 30.7% of non-squamous histology (8). Systemic therapy options have reflected this difference in biology, with pemetrexed chemotherapy and newer biologic agents targeting EGFR and ALK mutations showing greater efficacy in adenocarcinomas (especially those with identified mutations) compared to squamous cell carcinomas. However, the role of histology in primary tumor control is less clear, especially for small lesions where the local control rates often exceed 95%. While most studies do not specifically report local control based on histology, one retrospective study from Japan showed no difference in long-term local control, despite more rapid initial tumor shrinkage in lesions of squamous histology compared to adenocarcinomas of comparable size (26). This is likely due to the ablative nature of high doses of radiation employed during each fraction of SBRT, which engages different radiobiologic mechanisms for tumor cell damage that rely less on the linear quadratic equation and alpha/beta ratio that drive the relative radiosensitivity of squamous cell carcinomas. For larger lesions, however, we postulate that histology could play a role in local recurrence. In a pathologic study of mostly stage I NSCLC, adenocarcinomas evaluated at time of surgical pathology review had on average 2.5 mm of microscopic extension compared to only 1.1 mm in squamous cell carcinomas when matched for tumor diameter (27). It is therefore likely that tailoring local therapy better to histology, as well as biology such as mutational status, could result in improved local control.

Tumor location is primarily notable for increased risk of toxicity due to proximity to organs at risk (OAR). In one of the early publications of results with lung SBRT for early stage primary NSCLC, Indiana University reported increased grade 3-5 toxicity with treatment of central lesions (28), but this was in the setting of high doses of RT (60-66 Gy in 3 fractions). With data that BED_{10} ≥100 Gy provides excellent tumor control, we have employed 48 Gy in 4 fractions or 50 Gy in 5 fractions for large central lesions with minimal toxicity, reporting only one case of grade 3 esophagitis (14) and no other significant toxicity specific to central tumors. Peripheral lesions are at increased risk of rib fracture which was observed but not life threatening (17). While local failure is generally very low in patients with primary NSCLC in our studies so numbers are small, we did report local recurrence in 19% of central tumors (3 of 16 lesions) compared to only 2% in peripheral lesions (1 of 41) (16). There is conflicting evidence in the literature regarding local control of central tumors with some reports showing increased local failure rates (24), while others do not (29,30). The Cleveland Clinic recently reported very good local control (91.5% at 1.5 years) in lesions that were both large (>5 cm) and primarily central (68%) though this could also be explained by the predominance of squamous histology (67%) which may, in large lesions, be more radiosensitive and require narrower margins (29). Most studies of SBRT reflect the modern era of early stage lung cancer in which adenocarcinoma histology predominates due to the slow decline in smoking rates.

We initially found that younger age (<70 years) was a significant predictor of distant failure (14), though age did not correlate with worse OS in a Cox regression model when lesion size was accounted for. We subsequently reported a subset analysis of octogenarians which showed a higher 2-year OS of 74%, though these patients had slightly smaller tumors that were located more peripherally (96% *vs.* 4% centrally located) (15). While these patients could have also been more heavily selected for having fewer comorbidities, the cumulative risk of competing mortality was comparable to our prior publication (13% *vs.* 15%, respectively) (14). Other centers have also not reported differences in local control based on age alone (30). We reported no grade 3 or 4 toxicity in this elderly population (15). Therefore, the aggressive

nature of even early stage NSCLC coupled with the low risk of toxicity warrants treatment with SBRT in elderly patients.

We have also reported results comparing lung SBRT for primary lung cancer in the setting of presence or absence of pathologic confirmation and found no difference in local control or OS (16). Patients were well-matched for age, smoking history, and reason for receiving SBRT instead of surgery. Though patients with pathologically-confirmed lesions did have slightly earlier tumor stage than those without pathologic confirmation (T1 57% *vs.* 75%, respectively), mean tumor size was comparable (2.7 *vs.* 2.5 cm, respectively). There were no differences seen in 2-year local control (94% *vs.* 91%) or 2-year OS (64% *vs.* 65%) for patients with or without pathologic confirmation, respectively. Patients without pathologic confirmation were diagnosed radiographically based on progressive growth on CT scan or presence of hypermetabolic activity on PET/CT, with malignancy defined as maximum standardized uptake value SUV ≥2.5.

Intrapulmonary oligometastases

Our local control rates using SBRT for metastases to the lung is slightly lower than definitive SBRT for early stage primary NSCLC, with 2-year local control rates of 74-76% (17-19). This is consistent with prior reports (31), in which the limitation of SBRT is hypothesized to be dose, based on the observation that the histologies of many primaries that metastasize to lung are less radiosensitive than NSCLC. Our dataset was too small to perform subset analysis by histology, but 27% of the lesions were metastases from sarcoma or melanoma primaries, which generally have lower rates of local control with RT and may benefit from further dose escalation (18,32). Meanwhile, a recent retrospective review from Stanford found that colorectal primary was the most significant predictor of local failure in patients with oligometastatic disease (33), and 23% of metastatic lesions in our study were colorectal in origin. Given that studies showing BED_{10} >100 Gy were done in primary NSCLC, it seems reasonable to consider dose escalation in these patients, particularly for peripheral lesions. Another potential factor reducing the efficacy of SBRT in intrapulmonary metastases is local microscopic tumor spread, which contributes to positive margins in patients undergoing surgical resection, or lung metastasectomy, and is known to increase the risk of local recurrence (12).

In our study, local control greater than 12 months was significantly associated with improved distant control, and progression free survival was improved with a single lung metastasis compared to two or more lesions in the lung. These results are comparable to a large surgical series from the International Registry of Lung Metastases, in which 5,206 patients were treated with pulmonary metastasectomy (12). Our reported 2-year OS was 78% with median survival was 30 months, which are comparable to reports from other series (32,33). These survival rates often exceed those in early stage NSCLC, primarily due to relatively advanced age and comorbidities of patients diagnosed with NSCLC and undergoing SBRT, but further highlight the importance of durable local control in appropriately selected patients with oligometastatic disease. Multiple studies are ongoing to assess the role of SBRT to oligometastatic disease in extending survival.

Multiple primary lung cancers (MPLCs)

We have also employed SBRT in the treatment of MPLCs, which accounts for up to 4% of NSCLC (34). Our study of 18 patients included 6 patients with synchronous tumors and 12 patients with metachronous tumors, of which 27 lesions were treated with SBRT, 6 lesions were treated with prior fractionated RT, and 3 lesions had previously been resected (20). The vast majority of these patients (89%) were determined to be poor surgical candidates due to comorbid medical conditions and/or poor pulmonary reserve at time of SBRT. With median follow-up of 20 months, observed local control was 81%, and 2-year actuarial OS was 62%. Three of 6 deceased patients had developed metastatic disease. The challenge in MPLC is confirming the diagnosis of multiple primaries rather than metastases even from primary lung cancer. Criteria used still include those outlined by Martini and Melamed (35), though diagnosis is even more difficult in inoperable patients that we encounter for SBRT. Nonetheless, our local control was at least as good as what we have reported with treating single metastatic lesions in the lung (17,18).

No acute grade ≥2 toxicity was observed in our patients with MPLCs treated with SBRT. Clinical pneumonitis, as defined by cough and evidence of inflammation in the appropriate region on chest CT, was observed in 3 of 18 patients (17%) at 3, 4 and 8 months following completion of RT, and was the only late toxicity reported (20). Two of the 3 patients that developed pneumonitis had two centrally-located primary tumors. Surgical studies have noted that squamous tumors are more often centrally

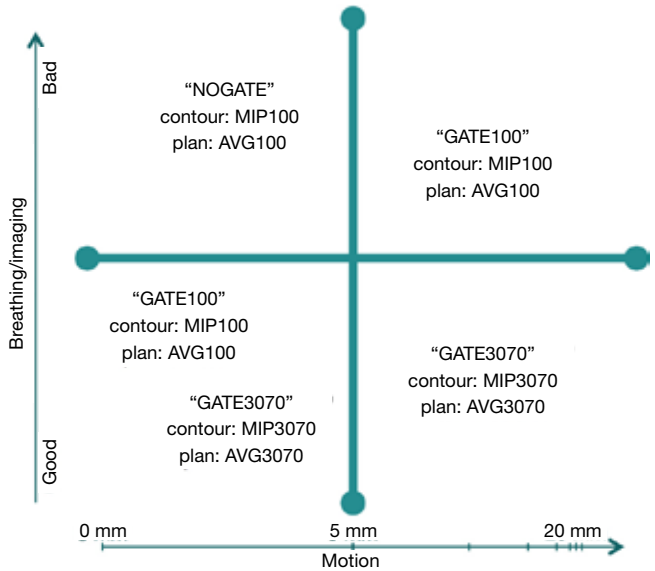


Figure 1 SBRT gating decision matrix. SBRT, stereotactic body radiotherapy.

located and associated with a local environment that is characterized by inflammatory changes (27), so it is postulated that histology more than central location drives risk of subsequent radiation pneumonitis. Fortunately symptoms resolved in all patients with administration of steroids.

Lung stereotactic body radiotherapy (SBRT) technique

Since the inception of UCSD's lung SBRT program in 2007, we have made several iterations to our technique. Here we describe our current technique, with brief commentary on these modifications. Patient immobilization consists of a customized airtight vacuum bag throughout the thorax, with a wing board and U-shaped handles to place the arms above the head. Use of abdominal compression for motion management has previously been noted to produce symptomatic chest wall discomfort, so we sought an imaging-based alternative (7). The Varian Respiratory Position Management System (RPM v.1.7.5, Varian Medical System, Palo Alto, CA, USA) is used to monitor respiration-induced tumor motion. The RPM reflector block is placed on the patient's abdomen (between the xiphoid process and umbilicus), and the position of the surrogate is monitored throughout the simulation process. Patients are instructed to breathe normally, avoiding deep breaths, sighing or talking. Video goggles were used initially to help guide patient respiration, but this process was discontinued after the system showed little to no benefit.

For the majority of patients, a 4-dimensional (4D) CT is performed on a 4-slice large bore scanner (QXi LightSpeed CT, GE Healthcare, Fairfield, CT), generating 10 phase-sorted CT image sets (0-90%, 2.5 mm slice thickness). The 0% phase image corresponds to maximum inspiration and the 50% phase image corresponds to maximum expiration. For patients that have not had an outside PET scan, a 4D PET/CT is performed on a 64-slice scanner (VCT LightSpeed, GE Healthcare) generating 5 phase-sorted PET images (10%, 30%, 50%, 70%, 90%, 3.3 mm slice thickness). As part of our 4D PET/CT protocol, a free-breathing CT scan for attenuation correction, a 3D PET (arms down) scan and 4D CT scan are also performed.

A medical physicist is present at the 4D simulation to characterize the respiration-induced tumor motion and decide on a gating strategy. The tumor position is observed in all 10 phase images, and the tumor motion is recorded in the superior-inferior, anterior-posterior and left-right directions. Based on the tumor motion and image quality, a decision is made to (I) gate with a ~50% duty cycle around expiration ("GATE3070"); (II) gate with a ~100% duty cycle throughout normal respiration ("GATE100"); or (III) treat independent of respiration ("NOGATE"). If a "GATE3070" technique is chosen (i.e., the gating window is set between the 30-70% respiratory phases), a maximum intensity projection (MIP) image and an average (AVG) image are created from the 30-70% respiratory phases as well. If a "GATE100" technique is chosen (i.e., the gating window is set for all phases of normal respiration), MIP and AVG images are created from all respiratory phases. The same images used for a "GATE100" technique can be used for a "NOGATE" technique. The decision matrix illustrated in *Figure 1* is used to help determine the most beneficial gating strategy.

Image registration, contouring and treatment planning are performed in Eclipse (v.10, Varian Medical Systems). The MIP image is fused with the diagnostic PET image and the corresponding 4D PET phase images (when available) for contouring the internal target volume (ITV). The lesion is first contoured using the mediastinal window, then the lung window is examined to ensure that the gross tumor volume (GTV) is not underestimated. The ITV to planning target volume (PTV) margin is typically set as 5 mm (isotropic). However, a larger margin of 8 mm is applied in the superior-inferior direction for tumors with large motion and significant imaging artifacts. 3D-CRT and static field

intensity modulated radiation therapy (IMRT) techniques have been used to create lung SBRT treatment plans, but volumetric arc therapy (VMAT) plans are the current standard of care at UCSD. Currently 1-2 arcs are used, with no entrance angles through the contralateral lung. Plans are normalized so that 100% of the ITV, and 95% of the PTV, are covered by the prescription dose. In addition, the ratios of the 100% and 50% isodose curve volumes to the PTV volume are also examined. Typical OAR include the lungs (minus the PTV), spinal cord, carina, heart, great vessels/aorta, esophagus, ribs, chest wall and skin.

Treatment verification on the linac is performed using the RPM, on-board imaging (OBI) and cone beam computed tomography (CBCT) systems (v.1.4, Varian Medical Systems). Patients are initially setup using the alignment lasers and tattoos given during the simulation. Orthogonal kilovoltage (kV) images are used to verify the alignment of the spinal structures near the target region, followed by CBCT to align the soft tissue and target location (when visible). The RPM trace guides are then set to the corresponding amplitude gating window (e.g., GATE3070 or GATE100), and a medical physicist verifies the stability of the respiratory trace prior to the start of treatment.

PET/CT in the post-SBRT setting

We have reported our findings using PET/CT scans for patients treated with SBRT for both primary NSCLC and metastatic lung tumors (19). Patients were followed by monthly clinical exam as well as imaging at 3-6 month intervals. The study involved blinding of the radiologist prior to re-review of all scans, including 86 PET/CT scans for 38 patients. Maximum standardized uptake value (SUV_{max}) thresholds have been proposed to guide identification of malignancy and tumor demarcation, such as SUV >2.5 (36) or >40% of the maximum SUV, but the universal validity of such thresholds is unclear (37). The mean pre-treatment SUV_{max} in our study was 4.95 for primary tumors, with this value decreasing by 47% on imaging 2-6 months post-treatment in patients that responded to treatment. While some reports suggest maximal response within 3 months, we advocate waiting until 6 months after SBRT for maximal SUV_{max} response. The mean SUV_{max} for metastatic lesions was 3.18, with response more variable than in primary lesions. The SUV was noted in metastatic lesions to even increase for as long as 6 months post-RT, with a decrease sometimes not seen until 10 months after treatment. Pre-SBRT SUV_{max} was noted to not correlate with local control or OS for either primary or metastatic lesions. In the absence of discrete SUV_{max} levels identified in this and other studies, we continue to use SUV_{max} >2.5 as a general guideline for active tumor (except for well-differentiated adenocarcinomas with are known to be poorly FDG-avid), though post-treatment comparison to pre-treatment values is most important in determining treatment respone. Generally we have adopted the strategy of waiting for two consecutive rises in SUV_{max} in patients with enlarging lesions on CT following SBRT to warrant treatment for recurrent disease, particularly in the setting of oligometastatic disease where apparent increases in activity are more common, unless patient shows significant clinical decline.

Conclusions

At UCSD we have applied a system of lung SBRT successfully to patients with primary NSCLC, intrapulmonary oligometastases, and MPLCs with high efficacy and low toxicity. Our technique maximizes patient comfort through absence of a body frame and fiducial markers in the tumor, instead employing a customized vacuum sealed bag for reproducible setup, and 4D-CT imaging at simulation coupled with OBI and an RPM system for motion management, based on the gating decision made at simulation. This technique is a reasonable alternative for patients that are inoperable or refuse surgery, with increasing data emerging to suggest efficacy may be equivalent to surgical resection. While patient selection is important, we found this treatment safe even in elderly patients. We are concerned that outcomes may be reduced in patients with large central lesions, and anticipate results from the ongoing RTOG 0813 trial to help determine maximum safe and effective dose for central tumors. Ultimately distant failure remains the greatest barrier to outcomes with larger, more advanced lesions. Systemic agents, particularly targeted biologic agents, appear promising and emphasize the importance of differentiating treatment based on biology to achieve better disease control. Meanwhile, we have begun to further shorten radiation treatment of very small peripheral lesions to single fraction SBRT, though will await the results of RTOG 0915 before applying single fraction routinely, particularly in >T1a lesions. Lung SBRT is also promising in the setting of oligometastatic disease, with properly selected patients living several years on modern systemic therapy,

and therefore increasing the importance of durable control for intrapulmonary lesions. Follow-up should include clinical exam, CT-based imaging, and PET particularly in patients with enlarging lesions on CT. Metastatic lesions in particular can have delayed response to RT, so caution with interpreting PET within 6 months of SBRT is advised. Ultimately multidisciplinary tumor board discussion for borderline cases is recommended.

Acknowledgements

None.

Footnote

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

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29.
2. Morrison R, Deeley TJ, Clelan WP. The Treatment of Carcinoma of the Bronchus: A Clinical Trial to Compare Surgery and Supervoltage Radiotherapy. Lancet 1963;281:683-4.
3. Bradley J, Graham MV, Winter K, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys 2005;61:318-28.
4. Kaskowitz L, Graham MV, Emami B, et al. Radiation therapy alone for stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1993;27:517-23.
5. Hayman JA, Martel MK, Ten Haken RK, et al. Dose escalation in non-small-cell lung cancer using three-dimensional conformal radiation therapy: update of a phase I trial. J Clin Oncol 2001;19:127-36.
6. Rosenzweig KE, Fox JL, Yorke E, et al. Results of a phase I dose-escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable nonsmall cell lung carcinoma. Cancer 2005;103:2118-27.
7. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 2003;124:1946-55.
8. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
9. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.
10. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100.
11. 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.
12. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 1997;113:37-49.
13. Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol 2009;27:1579-84.
14. Nath SK, Sandhu AP, Kim D, et al. Locoregional and distant failure following image-guided stereotactic body radiation for early-stage primary lung cancer. Radiother Oncol 2011;99:12-7.
15. Sandhu AP, Lau SK, Rahn D, et al. Stereotactic body radiation therapy in octogenarians with stage I lung cancer. Clin Lung Cancer 2014;15:131-5.
16. Haidar YM, Rahn DA 3rd, Nath S, et al. Comparison of outcomes following stereotactic body radiotherapy for non-small cell lung cancer in patients with and without pathological confirmation. Ther Adv Respir Dis 2014;8:3-12.
17. Nath SK, Sandhu AP, Jensen L, et al. Frameless image-guided stereotactic body radiation therapy for lung tumors with 4-dimensional computed tomography or 4-dimensional positron emission tomography/ computed tomography. Clin Lung Cancer 2011;12:180-6.
18. Kim D, Fuster MM, Nath SK, et al. Clinical outcomes following image-guided stereotactic body radiation for pulmonary oligometastases. J Radiosurgery & SBRT 2012;2:63-72.
19. Gill BS, Rivandi AH, Sandhu SP, et al. The role of positron emission tomography following radiosurgical treatment of malignant lung lesions. Nucl Med Commun 2012;33:607-12.
20. Rahn DA, Thakur S, Makani S, et al. Stereotactic body radiation therapy (SBRT) for multiple primary lung cancers (MPLC): a review and case series. J Radiosurgery & SBRT 2013;2:135-40.

21. Rowe BP, Boffa DJ, Wilson LD, et al. Stereotactic body radiotherapy for central lung tumors. J Thorac Oncol 2012;7:1394-9.
22. Zhang J, Yang F, Li B, et al. Which is the optimal biologically effective dose of stereotactic body radiotherapy for Stage I non-small-cell lung cancer? A meta-analysis. Int J Radiat Oncol Biol Phys 2011;81:e305-16.
23. Videtic GM, Stephans KL, Woody NM, et al. 30 Gy or 34 Gy? Comparing 2 single-fraction SBRT dose schedules for stage I medically inoperable non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2014;90:203-8.
24. Baumann P, Nyman J, Lax I, et al. Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer. A retrospective analysis of patients treated in the Nordic countries. Acta Oncol 2006;45:787-95.
25. Welter S, Theegarten D, Trarbach T, et al. Safety distance in the resection of colorectal lung metastases: a prospective evaluation of satellite tumor cells with immunohistochemistry. J Thorac Cardiovasc Surg 2011;141:1218-22.
26. Miyakawa A, Shibamoto Y, Kosaki K, et al. Early response and local control of stage I non-small-cell lung cancer after stereotactic radiotherapy: difference by histology. Cancer Sci 2013;104:130-4.
27. Giraud P, Antoine M, Larrouy A, et al. Evaluation of microscopic tumor extension in non-small-cell lung cancer for three-dimensional conformal radiotherapy planning. Int J Radiat Oncol Biol Phys 2000;48:1015-24.
28. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
29. Woody NM, Stephans KL, Marwaha G, et al. Stereotactic Body Radiation Therapy for Non-Small Cell Lung Cancer Tumors Greater Than 5 cm: Safety and Efficacy. Int J Radiat Oncol Biol Phys 2015;92:325-31.
30. Verstegen NE, Lagerwaard FJ, Hashemi SM, et al. Patterns of Disease Recurrence after SABR for Early Stage Non-Small-Cell Lung Cancer: Optimizing Follow-Up Schedules for Salvage Therapy. J Thorac Oncol 2015;10:1195-200.
31. Yamamoto T, Jingu K, Shirata Y, et al. Outcomes after stereotactic body radiotherapy for lung tumors, with emphasis on comparison of primary lung cancer and metastatic lung tumors. BMC Cancer 2014;14:464.
32. Norihisa Y, Nagata Y, Takayama K, et al. Stereotactic body radiotherapy for oligometastatic lung tumors. Int J Radiat Oncol Biol Phys 2008;72:398-403.
33. Binkley MS, Trakul N, Jacobs LR, et al. Colorectal Histology Is Associated With an Increased Risk of Local Failure in Lung Metastases Treated With Stereotactic Ablative Radiation Therapy. Int J Radiat Oncol Biol Phys 2015;92:1044-52.
34. Verhagen AF, Tavilla G, van de Wal HJ, et al. Multiple primary lung cancers. Thorac Cardiovasc Surg 1994;42:40-4.
35. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606-12.
36. Hong R, Halama J, Bova D, et al. Correlation of PET standard uptake value and CT window-level thresholds for target delineation in CT-based radiation treatment planning. Int J Radiat Oncol Biol Phys 2007;67:720-6.
37. Biehl KJ, Kong FM, Dehdashti F, et al. 18F-FDG PET definition of gross tumor volume for radiotherapy of non-small cell lung cancer: is a single standardized uptake value threshold approach appropriate? J Nucl Med 2006;47:1808-12.

Cite this article as: Gillespie EF, Atwood TF, Sandhu AP. Lung stereotactic body radiotherapy (SBRT): a single institution's outcomes and methodology in the context of a literature review. Transl Cancer Res 2015;4(4):372-380. doi: 10.3978/j.issn.2218-676X.2015.08.07

Stereotactic body radiation therapy in lung

Madhava R. Kanakamedala, Neil Duggar, Shankar P. Giri

Department of Radiation Oncology, University of Mississippi Medical Center, Jackson, MS, USA

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.

Correspondence to: Madhava R. Kanakamedala. Department of Radiation Oncology, University of Mississippi Medical Center, Jackson, MS, USA. Email: madkr2006@hotmail.com.

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 regiment, starting with 8 Gy ×3, and escalating to 10, 12, 14, 16, 18, 20 and 22 Gy ×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 ×3. In other tumor size groups, dose escalation was stopped prior to reaching the MTD (20-22 Gy ×3). Greater than 90% primary tumor control was observed with 20 Gy ×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 regiment, 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 disatant 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

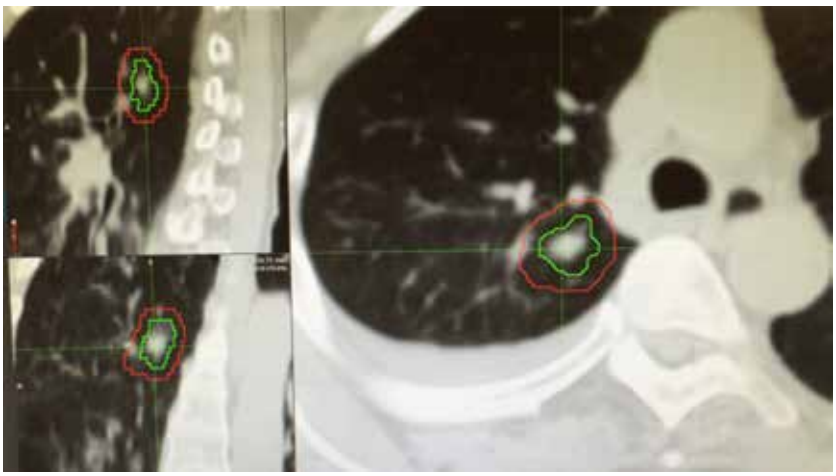


Figure 2 A three-view representation of the contours ITV (green) and PTV (red) for use in SBRT lung. The ITV was created by propagating the GTV contour from one phase of the respiratory cycle to all phases. The PTV was then created with a 5 mm expansion in all directions from the ITV. PTV, planning target 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	
$V_{90\%}$ ≥99%	99%
$V_{100\%}$ ≥95%	95%
Conformality	
$R_{100\%}$ ≤1.2	1.2
$R_{50\%}$	4.6
$R_{105\%}$ Outside of PTV ≤15%	15%
$D_{2\ cm}$	2,588 cGy
Normal tissues (constraints per protocol)	
Spinal cord, max dose	3,000 cGy
Spinal cord, $V_{2,250\ cGy}$ ≤0.25 cc	0.25 cc
Spinal cord, $V_{1,350\ Gy}$ ≤0.5 cc	0.50 cc
Esophagus, max dose	5,250 cGy
Esophagus, $V_{2,750\ cGy}$ ≤5 cc	5.00 cc
Ipsilateral brachial plexus, max dose	3,200 cGy
Ipsilateral brachial plexus, $V_{3,000\ cGy}$ ≤3 cc	3.00 cc
Trachea and ipsilateral bronchus, max dose	5,250 cGy
Trachea and ipsilateral bronchus, $V_{1,800\ cGy}$ ≤4 cc	4.00 cc
Great vessels, max dose	5,250 cGy
Great vessels, $V_{4,700\ cGy}$ ≤10 cc	10 cc
Heart/pericardium, max dose	5,250 cGy
Heart/pericardium, $V_{3,200\ cGy}$ ≤15 cc	15.00 cc
Whole lung-GTV, $V_{20\ Gy}$ <10%	10%
Whole lung-GTV, $V_{1,250\ cGy}$ ≤1,500 cc	1,500 cc
Whole lung-GTV, $V_{1,350\ cGy}$ ≤1,000 cc	1,000 cc
Skin, max dose	3,200 cGy
Skin, $V_{3,000\ cGy}$ ≤10 cc	10.00 cc
Ribs, $V_{3,200\ cGy}$ ≤1 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

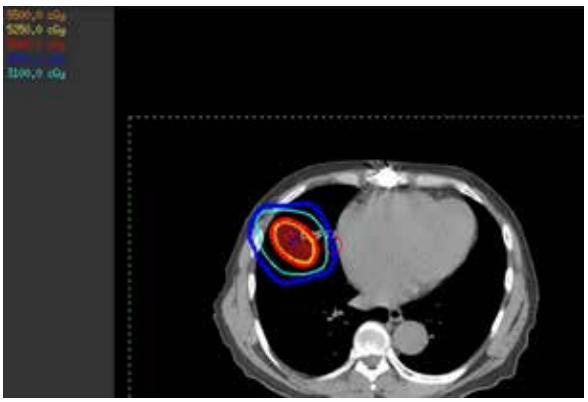


Figure 3 An axial cut of a characteristic dose distribution for lung SBRT delivered using a linear accelerator and MLC via two coplanar arcs. SBRT, stereotactic body radiation therapy; MLC, multi-leaf collimator.

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.

References

1. Raz DJ, Zell JA, Ou SH, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. Chest 2007;132:193-9.
2. Haffty BG, Goldberg NB, Gerstley J, et al. Results of radical radiation therapy in clinical stage I, technically operable non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1988;15:69-73.
3. Sibley GS, Jamieson TA, Marks LB, et al. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. Int J Radiat Oncol Biol Phys 1998;40:149-54.
4. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
5. Krol AD, Aussems P, Noordijk EM, et al. Local irradiation alone for peripheral stage I lung cancer: could we omit the elective regional nodal irradiation? Int J Radiat Oncol Biol Phys 1996;34:297-302.
6. Williams TE, Thomas CR Jr, Turrisi AT 3rd. Counterpoint: better radiation treatment of non-small cell lung cancer using new techniques without elective nodal irradiation. Semin Radiat Oncol 2000;10:315-23.
7. Robertson JM, Ten Haken RK, Hazuka MB, et al. Dose escalation for non-small cell lung cancer using conformal radiation therapy. Int J Radiat Oncol Biol Phys 1997;37:1079-85.
8. Bradley J, Graham MV, Winter K, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys 2005;61:318-28.
9. Slotman BJ, Antonisse IE, Njo KH. Limited field irradiation in early stage (T1-2N0) non-small cell lung cancer. Radiother Oncol 1996;41:41-4.
10. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 2003;124:1946-55.
11. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a

phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
12. Hall EJ. Radiobiology for the Radiologist. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2000.
13. Kolesnick R, Fuks Z. Radiation and ceramide-induced apoptosis. Oncogene 2003;22:5897-906.
14. Henry B, Möller C, Dimanche-Boitrel MT, et al. Targeting the ceramide system in cancer. Cancer Lett 2013;332:286-94.
15. Danial NN, Korsmeyer SJ. Cell death: critical control points. Cell 2004;116:205-19.
16. Garcia-Barros M, Paris F, Cordon-Cardo C, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science 2003;300:1155-9.
17. Rusthoven KE, Hammerman SF, Kavanagh BD, et al. Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis. Acta Oncol 2009;48:578-83.
18. Iyengar P, Kavanagh BD, Wardak Z, et al. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. J Clin Oncol 2014;32:3824-30.
19. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e211S-50S.
20. Pretreatment evaluation of non-small-cell lung cancer. The American Thoracic Society and The European Respiratory Society. Am J Respir Crit Care Med 1997;156:320-32.
21. Dwamena BA, Sonnad SS, Angobaldo JO, et al. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s--meta-analytic comparison of PET and CT. Radiology 1999;213:530-6.
22. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. Chest 2003;123:137S-146S.
23. Silvestri GA, Gould MK, Margolis ML, et al. Noninvasive staging of non-small cell lung cancer: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest 2007;132:178S-201S.
24. Birim O, Kappetein AP, Stijnen T, et al. Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer. Ann Thorac Surg 2005;79:375-82.
25. Gould MK, Kuschner WG, Rydzak CE, et al. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. Ann Intern Med 2003;139:879-92.
26. Schrevens L, Lorent N, Dooms C, et al. The role of PET scan in diagnosis, staging, and management of non-small cell lung cancer. Oncologist 2004;9:633-43.
27. Bunyaviroch T, Coleman RE. PET evaluation of lung cancer. J Nucl Med 2006;47:451-69.
28. Takamochi K, Yoshida J, Murakami K, et al. Pitfalls in lymph node staging with positron emission tomography in non-small cell lung cancer patients. Lung Cancer 2005;47:235-42.
29. Schmidt-Hansen M, Baldwin DR, Hasler E, et al. PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer. Cochrane Database Syst Rev 2014;11:CD009519.
30. Lardinois D, Weder W, Hany TF, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. N Engl J Med 2003;348:2500-7.
31. Reed CE, Harpole DH, Posther KE, et al. Results of the American College of Surgeons Oncology Group Z0050 trial: the utility of positron emission tomography in staging potentially operable non-small cell lung cancer. J Thorac Cardiovasc Surg 2003;126:1943-51.
32. Micames CG, McCrory DC, Pavey DA, et al. Endoscopic ultrasound-guided fine-needle aspiration for non-small cell lung cancer staging: A systematic review and metaanalysis. Chest 2007;131:539-48.
33. Puli SR, Batapati Krishna Reddy J, Bechtold ML, et al. Endoscopic ultrasound: it's accuracy in evaluating mediastinal lymphadenopathy? A meta-analysis and systematic review. World J Gastroenterol 2008;14:3028-37.
34. Prenzel KL, Mönig SP, Sinning JM, et al. Lymph node size and metastatic infiltration in non-small cell lung cancer. Chest 2003;123:463-7.
35. Catalano MF, Sivak MV Jr, Rice T, et al. Endosonographic features predictive of lymph node metastasis. Gastrointest Endosc 1994;40:442-6.
36. Bhutani MS, Hawes RH, Hoffman BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration for diagnosis of malignant lymph node invasion. Gastrointest Endosc 1997;45:474-9.
37. Kramer H, Groen HJ. Current concepts in the mediastinal

lymph node staging of nonsmall cell lung cancer. Ann Surg 2003;238:180-8.
38. Rule WG, Jain S, Boike TP. Stereotactic body radiation therapy. In: Khan FM, Gerbi BJ, eds. Treatment Planning in Radiation Oncology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2012:278-97.
39. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys 2010;37:4078-101.
40. Khan FM, Gibbons JP. The physics of radiation therapy. 5th ed. Philadelphia, PA: Lippincott, Williams, and Wilkins, 2014:18.
41. Solberg TD, Balter JM, Benedict SH, et al. Quality and safety considerations in stereotactic radiosurgery and stereotactic body radiation therapy: Executive summary. Pract Radiat Oncol 2012;2:2-9.
42. Bova, F J. Cranial Radiosurgery. Treatment Planning in Radiation Oncology. Ed. FM Khan and BJ Gerbi. 3rd. Philadelphia: Lippincott Williams & Wilkins, 2012:259-77.
43. Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. Med Phys 2006;33:3874-900.
44. Fuss M, Salter BJ, Rassiah P, et al. Repositioning accuracy of a commercially available double-vacuum whole body immobilization system for stereotactic body radiation therapy. Technol Cancer Res Treat 2004;3:59-67.
45. Blomgren H, Lax I, Göranson H, et al. Radiosurgery for Tumors in the Body: Clinical Experience Using a New Method. Journal of Radiosurgery 1998;1:63-74.
46. Wulf J, Hädinger U, Oppitz U, et al. Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame. Radiother Oncol 2000;57:225-36.
47. Abdelnour AF, Nehmeh SA, Pan T, et al. Phase and amplitude binning for 4D-CT imaging. Phys Med Biol 2007;52:3515-29.
48. Li H, Noel C, Garcia-Ramirez J, et al. Clinical evaluations of an amplitude-based binning algorithm for 4DCT reconstruction in radiation therapy. Med Phys 2012;39:922-32.
49. Didierlaurent D, Ribes S, Batatia H, et al. The retrospective binning method improves the consistency of phase binning in respiratory-gated PET/CT. Phys Med Biol 2012;57:7829-41.
50. Castillo SJ, Castillo R, Castillo E, et al. Evaluation of 4D CT acquisition methods designed to reduce artifacts. J Appl Clin Med Phys 2015;16:4949.
51. Cerviño LI, Chao AK, Sandhu A, et al. The diaphragm as an anatomic surrogate for lung tumor motion. Phys Med Biol 2009;54:3529-41.
52. Tian Y, Wang Z, Ge H, et al. Dosimetric comparison of treatment plans based on free breathing, maximum, and average intensity projection CTs for lung cancer SBRT. Med Phys 2012;39:2754-60.
53. Ehler ED, Tomé WA. Lung 4D-IMRT treatment planning: an evaluation of three methods applied to four-dimensional data sets. Radiother Oncol 2008;88:319-25.
54. Liu J, Wang JZ, Zhao JD, et al. Use of combined maximum and minimum intensity projections to determine internal target volume in 4-dimensional CT scans for hepatic malignancies. Radiat Oncol 2012;7:11.
55. Grosu AL, Piert M, Weber WA, et al. Positron emission tomography for radiation treatment planning. Strahlenther Onkol 2005;181:483-99.
56. de Figueiredo BH, Antoine M, Trouette R, et al. Use of FDG-PET to guide dose prescription heterogeneity in stereotactic body radiation therapy for lung cancers with volumetric modulated arc therapy: a feasibility study. Radiat Oncol 2014;9:300.
57. Rong Y, Bazan JG, Sekhon A, et al. Minimal Inter-Fractional Fiducial Migration during Image-Guided Lung Stereotactic Body Radiotherapy Using SuperLock Nitinol Coil Fiducial Markers. PLoS One 2015;10:e0131945.
58. Nuyttens JJ, Prévost JB, Praag J, et al. Lung tumor tracking during stereotactic radiotherapy treatment with the CyberKnife: Marker placement and early results. Acta Oncol 2006;45:961-5.
59. International Commission on Radiation Units and Measurements. ICRU Report 83 Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT). Journal of the ICRU 10.1, 2010.
60. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 1989;62:679-94.
61. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004;101:1623-31.
62. Kirkpatrick JP, Meyer JJ, Marks LB. The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery. Semin Radiat Oncol 2008;18:240-3.
63. Emami B. Tolerance of normal tissue to therapeutic radiation. Reports of Radiotherapy and Oncology 2013;1:35-48.
64. Ong CL, Verbakel WF, Cuijpers JP, et al. Stereotactic

radiotherapy for peripheral lung tumors: a comparison of volumetric modulated arc therapy with 3 other delivery techniques. Radiother Oncol 2010;97:437-42.
65. Bortfeld T, Jiang SB, Rietzel E. Effects of motion on the total dose distribution. Semin Radiat Oncol 2004;14:41-51.
66. Rao M, Wu J, Cao D, et al. Dosimetric impact of breathing motion in lung stereotactic body radiotherapy treatment using intensity modulated radiotherapy and volumetric modulated arc therapy [corrected]. Int J Radiat Oncol Biol Phys 2012;83:e251-6.
67. McGrath SD, Matuszak MM, Yan D, et al. Volumetric modulated arc therapy for delivery of hypofractionated stereotactic lung radiotherapy: A dosimetric and treatment efficiency analysis. Radiother Oncol 2010;95:153-7.
68. Brock J, Bedford J, Partridge M, et al. Optimising stereotactic body radiotherapy for non-small cell lung cancer with volumetric intensity-modulated arc therapy--a planning study. Clin Oncol (R Coll Radiol) 2012;24:68-75.
69. Ong C, Verbakel WF, Cuijpers JP, et al. Dosimetric impact of interplay effect on RapidArc lung stereotactic treatment delivery. Int J Radiat Oncol Biol Phys 2011;79:305-11.
70. Tajima Y, Nakayama H, Itonaga T, et al. Dosimetric evaluation of compensator intensity modulation-based stereotactic body radiotherapy for Stage I non-small-cell lung cancer. Br J Radiol 2015;88:20150122.
71. Wang Z, Kong QT, Li J, et al. Clinical outcomes of cyberknife stereotactic radiosurgery for lung metastases. J Thorac Dis 2015;7:407-12.
72. Bahig H, Campeau MP, Vu T, et al. Predictive parameters of CyberKnife fiducial-less (XSight Lung) applicability for treatment of early non-small cell lung cancer: a single-center experience. Int J Radiat Oncol Biol Phys 2013;87:583-9.
73. Arcangeli S, Agolli L, Portalone L, et al. Patterns of CT lung injury and toxicity after stereotactic radiotherapy delivered with helical tomotherapy in early stage medically inoperable NSCLC. Br J Radiol 2015;88:20140728.
74. Casutt A, Bouchaab H, Beigelman-Aubry C, et al. Stereotactic body radiotherapy with helical TomoTherapy for medically inoperable early stage primary and second-primary non-small-cell lung neoplasm: 1-year outcome and toxicity analysis. Br J Radiol 2015;88:20140687.
75. Hrbacek J, Lang S, Graydon SN, et al. Dosimetric comparison of flattened and unflattened beams for stereotactic ablative radiotherapy of stage I non-small cell lung cancer. Med Phys 2014;41:031709.
76. Li X, Yang Y, Li T, et al. Dosimetric effect of respiratory motion on volumetric-modulated arc therapy-based lung SBRT treatment delivered by TrueBeam machine with flattening filter-free beam. J Appl Clin Med Phys 2013;14:4370.
77. Corradetti MN, Haas AR, Rengan R. Central-airway necrosis after stereotactic body-radiation therapy. N Engl J Med 2012;366:2327-9.

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

Current Evidence

The factors affecting local tumor control after stereotactic body radiotherapy for non-small cell lung cancer

Satoru Ochiai[1], Yasufumi Yamashita[1], Yoshihito Nomoto[2]

[1]Department of Radiation Oncology, Matsusaka Central Hospital, Matsusaka, Japan; [2]Department of Radiology, Mie University School of Medicine, Tsu, Japan

Correspondence to: Satoru Ochiai, MD. Department of Radiation Oncology, Matsusaka Central Hospital, 102 Kobou Kawai-machi, Matsusaka, Mie 515-8566, Japan. Email: sochiai1981@gmail.com.

Submitted Sep 28, 2015. Accepted for publication Oct 01, 2015.
doi: 10.3978/j.issn.2218-676X.2015.10.08
View this article at: http://dx.doi.org/10.3978/j.issn.2218-676X.2015.10.08

Stereotactic body radiotherapy (SBRT), also called stereotactic ablative radiotherapy (SABR), has been widely used as an effective treatment for early-stage lung cancer, especially in medically inoperable cases (1,2). The local control (LC) rates after SBRT for early-stage non-small cell lung cancer (NSCLC) have been reported to be 85-98% (1). Although the treatment results seem to be favorable, several risk factors for local tumor progression have been reported. Here, we would like to summarize and discuss about reported factors that affect local tumor control after SBRT.

Tumor stage

Tumor stage is one of the most well recognized risk factor for local tumor progression after SBRT. Onimaru *et al*. analyzed the treatment results of 41 patients with stage I NSCLC (25 with T1 and 16 with T2 tumor) treated by SBRT (3). The dose fractionation schedule of SBRT was 40 or 48 Gy in 4 fractions within 1 week. They reported that T stage was a significant factor for LC in multivariate analysis. Dunlap *et al*. compared the LC rates of 40 patients with peripheral T1 and T2 NSCLC treated with SBRT (4). SBRT was delivered at a median dose of 60 Gy in 3 or 5 fractions. Increasing tumor size correlated with worse LC. LC at 2 years was 90% and 70% in T1 and T2 tumors, respectively (P=0.03). Matsuo *et al*. investigated the factors that influence clinical outcomes after SBRT for NSCLC (5). A total of 101 patients underwent SBRT with 48 Gy in 4 fractions were evaluated. Factors including age, maximum tumor diameter, sex, performance status, operability, histology, and overall treatment time were evaluated. Tumor diameter was the only significant factor for local progression in a Cox proportional hazards model. Shirata *et al*. investigated the prognostic factors for LC of stage I NSCLC in SBRT (6). Eighty patients (81 lesions) treated with 3 dose levels, 48 Gy in 4 fractions, 60 Gy in 8 fractions and 60 Gy in 15 fractions were evaluated. The 3-year LC rates were 89.0% with T1 tumors and 64.8% in those with T 2 tumors (log-rank P=0.001) and T factor was shown to be a significant factor for LC with a Cox proportional hazard model analysis (P=0.013).

These findings indicate that T2 tumor, compared with T1 tumor, is the risk factor for local progression after SBRT for early-stage NSCLC.

The maximum standardized uptake value (SUVmax) on F18-fluorodeoxyglucose positron emission tomography (FDG-PET)

Pre-treatment SUVmax of primary tumor on FDG-PET is also described predictive factor for LC after SBRT in several reports. Takeda *et al*. evaluated the relationship between SUVmax on FDG-PET of 95 patients with 97 tumors and local recurrence (7). By multivariate analysis, the SUVmax of a primary tumor was the only predictive factor for local recurrence (P=0.002). Two-year LC rates for lower SUV-max (less than 6.0) and higher SUV-max (6.0 or more) were 93% and 42%, respectively. Clarke *et al*. investigated if SUVmax on pre-treatment FDG-PET would predict clinical outcome after SBRT for early-stage NSCLC (8). Eighty two patients who were evaluated with FDG-PET before SBRT were analyzed. On univariate

analysis SUVmax predicted for local failure (P=0.044). Na *et al.* reported a meta-analysis of prediction value of SUVmax for the outcome in NSCLC receiving radiotherapy (9). In the analysis of SBRT group, hazard ratio for LC was reported to be 1.11 (95% confidence interval, 1.06-1.18) for SUVmax of pre-treatment FDG-PET.

Although the optimal cut-off value of SUVmax is still controversial, "high" primary tumor SUVmax seemed to be a risk factor for local tumor progression.

Overall treatment time of SBRT

Kestin *et al.* investigated the factors that affect the clinical outcome for lung SBRT (10). Five hundred five tumors in 483 patients with clinical stage T1-T2N0 NSCLC treated with SBRT at 5 institutions were evaluated. In their analysis, overall treatment time of SBRT correlated to 2-year local recurrence. Two-year local tumor progression rates for longer overall treatment time of SBRT (11 or more elapsed days) and shorter overall treatment time (less than 10 days) were 14% and 4%, respectively (P<0.01). The longer overall treatment time might have a negative effect on the outcome after SBRT.

Dose-response relationship

The applicability of biologically equivalent dose (BED) employing a large dose per fraction is criticized by the likelihood overestimating the BED (11). However many clinicians often use the linear-quadratic (LQ) model and BED to estimate the effects of various radiation schedules. It has been also reported that the LQ model fits the radiation response of epithelial tissues <23 Gy per fraction (12). Onishi *et al.* reported multicenter retrospective study of SBRT for stage I NSCLC (13). Two hundred fifty five patients were analyzed and the median BED 10 was 111 Gy (range, 57-180 Gy). The local tumor progression rate was 8.4% for a BED of 100 Gy or more compared with 42.9% for less than 100 Gy (P<0.001). Kestin *et al.* examined dose-response relationships with various NSCLC SBRT fraction regimens (10). Five hundred five tumors in 483 patients with clinical stage T1-T2N0 NSCLC treated with SBRT at 5 institutions were evaluated. Median prescription BED 10 was 132 Gy (50.4-180). Two-year local recurrence rates were 4% and 15% for BED10 >105 Gy and BED <105 Gy, respectively (P<0.01). According to these findings, BED 100 Gy or more generally seemed to be necessary for SBRT in order to achieve a more than 90% LC rate.

Dose-escalation

Although the LC rate of small tumor after SBRT seemed to be excellent, that of larger tumor, such as T2 tumor, is not still unsatisfied. Davis *et al.* reported the clinical outcome of patients with T1-T2N0M0 and treated with SBRT. The RSSearch® Patient Registry was screened for 723 patients (517 with T1 and 244 with T2) (14). Median SBRT dose was 54 Gy (range, 10-80 Gy) delivered in a median of 3 fractions (range, 1-5), and median BED10 was 151.2 Gy (range, 20-240 Gy). LC was associated with higher BED10 for T2 tumors. Seventeen-month LC rate for T2 tumors treated with BED10 <105 Gy, BED10 105-149, and BED10 150 or more was 43%, 74%, and 95% respectively (P=0.011). On the other hand, there was not significant association between higher BED10 and T1 tumors. These results indicate that dose-escalation in SBRT might be beneficial for the treatment of larger tumor. On the other hand, Mehta *et al.* reported that dose-escalation beyond a BED10 of 159 Gy likely translates to a clinically insignificant gain in tumor control probability but may result in clinically significant toxicity (15). Zhang *et al.* reported a meta-analysis of SBRT for stage I NSCLC (16). BED was divided into four groups: low (<83.2 Gy), medium (83.2-106 Gy), medium to high (106-146 Gy), high (>146 Gy) and the treatment outcome was evaluated. The overall survival for the medium or medium to high BED groups was higher than those for the low or high BED groups. Therefore medium or medium to high BED (range, 83.2-146 Gy) was indicated to be more beneficial and reasonable BED. Thus, careful attention should be paid in case of dose-escalation of SBRT for early-stage NSCLC.

Recently, the results of JCOG0702 trial (multicenter phase I study of SBRT for T2N0M0 NSCLC with planning target volume <100 cc) were reported (17). The dose of SBRT was prescribed at D95 of the PTV. The recommend dose was determined to be 55 Gy in 4 fractions in the study. Further prospective studies are needed to determine whether dose-escalated SBRT improve clinical outcomes.

Centrally located tumor

Timmerman *et al.* reported a phase II study of SBRT for medically inoperable stage I NSCLC (18). SBRT treatment dose was 60 to 66 Gy total in 3 fractions. In their study, SBRT for central tumors was associated with a greater than 10-fold increase risk of high grade toxicity or death. According to the results, SBRT with high dose for centrally

located tumor has been considered to be risky. On the other hand, several investigators have reported favorable outcomes and toxicity profiles with moderate dose of SBRT (19).

Recently, Davis *et al*. reported treatment patterns and outcomes of SBRT for centrally located NSCLC or lung metastases from the RSSearch® (20). One hundred eleven patients with 114 centrally located lung tumors (48 T1-T2N M0 NSCLC) were evaluated. Median dose to centrally located NSCLC was 48 Gy and median BED10 was 105.6 Gy. Two-year LC rate was 76.4% and toxicity was low with no grade 3 or higher acute or late toxicities.

JROSG10-1 and RTOG0813 are dose escalation studies of SBRT for centrally located stage I NSCLC. Data from these trials will provide prospective date to determine the feasibility and optimal dose fractionation of SBRT for these tumors.

In summary, SBRT has been considered as highly effective treatment for early-stage NSCLC. However, there are still many unsolved issues, such as optimal dose fractionation or tolerable dose of normal organs. Further studies are warranted to provide the optimal treatment.

Acknowledgements

None.

Footnote

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

References

1. Nagata Y. Stereotactic body radiotherapy for early stage lung cancer. Cancer Res Treat 2013;45:155-61.
2. Onishi H, Araki T. Stereotactic body radiation therapy for stage I non-small-cell lung cancer: a historical overview of clinical studies. Jpn J Clin Oncol 2013;43:345-50.
3. Onimaru R, Fujino M, Yamazaki K, et al. Steep dose-response relationship for stage I non-small-cell lung cancer using hypofractionated high-dose irradiation by real-time tumor-tracking radiotherapy. Int J Radiat Oncol Biol Phys 2008;70:374-81.
4. Dunlap NE, Larner JM, Read PW, et al. Size matters: a comparison of T1 and T2 peripheral non-small-cell lung cancers treated with stereotactic body radiation therapy (SBRT). J Thorac Cardiovasc Surg 2010;140:583-9.
5. Matsuo Y, Shibuya K, Nagata Y, et al. Prognostic factors in stereotactic body radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2011;79:1104-11.
6. Shirata Y, Jingu K, Koto M, et al. Prognostic factors for local control of stage I non-small cell lung cancer in stereotactic radiotherapy: a retrospective analysis. Radiat Oncol 2012;7:182.
7. Takeda A, Yokosuka N, Ohashi T, et al. The maximum standardized uptake value (SUVmax) on FDG-PET is a strong predictor of local recurrence for localized non-small-cell lung cancer after stereotactic body radiotherapy (SBRT). Radiother Oncol 2011;101:291-7.
8. Clarke K, Taremi M, Dahele M, et al. Stereotactic body radiotherapy (SBRT) for non-small cell lung cancer (NSCLC): is FDG-PET a predictor of outcome? Radiother Oncol 2012;104:62-6.
9. Na F, Wang J, Li C, et al. Primary tumor standardized uptake value measured on F18-Fluorodeoxyglucose positron emission tomography is of prediction value for survival and local control in non-small-cell lung cancer receiving radiotherapy: meta-analysis. J Thorac Oncol 2014;9:834-42.
10. Kestin L, Grills I, Guckenberger M, et al. Dose-response relationship with clinical outcome for lung stereotactic body radiotherapy (SBRT) delivered via online image guidance. Radiother Oncol 2014;110:499-504.
11. Park C, Papiez L, Zhang S, et al. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. Int J Radiat Oncol Biol Phys 2008;70:847-52.
12. Fowler JF, Tomé WA, Fenwick JD, et al. A challenge to traditional radiation oncology. Int J Radiat Oncol Biol Phys 2004;60:1241-56.
13. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100.
14. Davis JN, Medbery C 3rd, Sharma S, et al. Stereotactic body radiotherapy for early-stage non-small cell lung cancer: clinical outcomes from a National Patient Registry. J Radiat Oncol 2015;4:55-63.
15. Mehta N, King CR, Agazaryan N, et al. Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lungcancer: A pooled analysis of biological equivalent dose and local control. Pract Radiat Oncol 2012;2:288-95.
16. Zhang J, Yang F, Li B, et al. Which is the optimal

biologically effective dose of stereotactic body radiotherapy for Stage I non-small-cell lung cancer? A meta-analysis. Int J Radiat Oncol Biol Phys 2011;81:e305-16.
17. Onimaru R, Shirato H, Shibata T, et al. Phase I study of stereotactic body radiation therapy for peripheral T2N0M0 non-small cell lung cancer with PTV<100cc using a continual reassessment method (JCOG0702). Radiother Oncol 2015;116:276-80.
18. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
19. Senthi S, Haasbeek CJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol 2013;106:276-82.
20. Davis JN, Medbery C, Sharma S, et al. Stereotactic body radiotherapy for centrally located early-stage non-small cell lung cancer or lungmetastases from the RSSearch(®) patient registry. Radiat Oncol 2015;10:113.

Cite this article as: Ochiai S, Yamashita Y, Nomoto Y. The factors affecting local tumor control after stereotactic body radiotherapy for non-small cell lung cancer. Transl Cancer Res 2015;4(5):574-577. doi: 10.3978/j.issn.2218-676X.2015.10.08

Current Evidence

Are three doses of stereotactic ablative radiotherapy (SABR) more effective than 30 doses of conventional radiotherapy?

Anna O. Simeonova, Katharina Fleckenstein, Hansjörg Wertz, Anian Frauenfeld, Judit Boda-Heggemann, Frank Lohr, Frederik Wenz

Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany

Correspondence to: Anna O. Simeonova, MD. Department of Radiation Oncology, University Medical Center Mannheim, Theodor-Kutzer Ufer 1-3,68167 Mannheim, Germany. Email: anna.simeonova@gmail.com.

Abstract: In early stage non-small cell lung cancer (NSCLC) definitive radiation therapy is an appropriate alternative to surgery. Recent studies show, that in such patients hypofractionation schedules (for example 3 times 18 Gy or 5 times 12 Gy), can be safely applied, without causing severe toxicities and achieving high local control rates of up to 90% and more. In the last couple of years a lot of knowledge about the cancer biology, technical aspects, clinical outcomes and toxicities has been accumulated from different clinical trials. The purpose of this review is to summarize recent outcomes and developments in stereotactic radiation therapy for patients with early stage NSCLC.

Keywords: Non-small cell lung cancer; stereotactic ablative radiotherapy

Submitted Oct 17, 2011. Accepted for publication Oct 24, 2011.
doi: 10.3978/j.issn.2218-6751.10.01
View this article at: http://www.tlcr.org/article/view/263/553

Introduction

Lung cancer continues to be the leading cause of cancer-related mortality in men and women, whereby the rates recently showed a significant decline in women after continuously increasing since the 1930s (1). For stage I non-small cell lung cancer (NSCLC), surgery alone results typically in a 5-year overall survival (OS) of 60-70% (2).

For patients with stage I NSCLC who cannot undergo radical resection e.g., for medical reasons, definitive radiation therapy is the appropriate alternative to surgery. For these patients standard fractionated radiotherapy alone can lead to a 5-year OS of 8-15% and a cancer specific survival rate in the range of 30-55% (due to competing risks of death) (3,4). Recent publications also support the strategy of treating only the primary tumor and PET positive lymph nodes (involved node radiotherapy; INRT) instead of treating the elective nodal regions (elective nodal irradiation; ENI) to reduce the volume of irradiated healthy tissue especially keeping the volume of lung that receives more than 20 Gray (Gy) below 35% (using conventional fractionation) (5-8). However, local tumor control after a conventional treatment with 55 to 70 Gy delivered over 4 to 7 weeks is as shown above suboptimal. Available data suggest that conventionally fractionated doses of >70 Gy might be necessary to control >90% of tumors locally (9-11).

Already in 1995, Blomgren *et al.* showed improved local control rates for patients with lung cancer treated with stereotactic hypofractionated radiotherapy compared with conventionally fractionated radiation (9). After a phase of careful dose escalation, single dose treatments at doses of 30 Gy (12) and fractionated treatments with 5×10^{-12} Gy or 3 times 20 Gy are currently applied on various institutional protocols and seem to be reasonably safe, with increase of the tumor control (SBRT prescription of 60 Gy in 3 fractions equates to as much as 150 Gy delivered in conventional fractions) (10,11,13).

The aim of this review is to summarize the updates of the radiobiology, technical aspects and clinical outcomes of SBRT.

SABR/SBRT

Stereotactic body radiation therapy (SBRT) or SABR (stereotactic ablative radiotherapy) is a relatively novel concept in which high doses of radiation are directed focally onto malignant lesions in organ sites other than the brain,

including lung, liver, and spine tumors. The idea of SBRT is derived from the experience in treating metastatic lesions in the brain by SRS (stereotactic radiosurgery). In SRS very high radiation doses are delivered to small brain lesions in a single session, with the intent to ablate all malignant tumor cells in one setting. The success rates of this treatment approach, with local tumor control rates as high as 93.3%, have made SRS a standard of care for limited metastatic disease to the brain (14-16).

SBRT as discussed here will largely adhere to the accepted definition in the United States as the delivery of high-dose focused radiation in one to five fractions onto small malignant lesions. High-dose delivery is most often understood as single fraction doses exceeding 5 Gy. Small lesions are most often defined as being less than 5 cm in maximum diameter. Focal radiation delivery refers to narrow planning target volume (PTV) margins added to a target volume delineated in consecutive slices of a CT, MRI or PET radiation planning dataset. Additionally, SBRT is a radiation therapy modality for which a target has to be directly or indirectly localized before the radiation dose is delivered.

Steep dose gradients between the lung lesions and surrounding normal tissue are a hallmark of SBRT dose distributions, and achieve excellent normal tissue sparing. This is accomplished by using multiple radiation beams which are shaped according to the tumor outline, and are all centered upon the lesion. While each of the radiation beams delivers a small fraction of the cumulative radiation dose, the dose at the target, where all radiation beams intersect, is summing up to high tumoricidal dose levels. Similar dose concentration can be achieved using arc delivery techniques during which a multi-leaf collimator, a radiation beam shaping device, continually adjusts the radiation port to the shape of the target from a given beam's eye view. SBRT radiation plans use 7 to 11 individual radiation beams arranged coplanar or non-coplanar around the target lesion, with little incremental plan quality gained when the number of radiation ports exceeds 9 (17-21).

Extracranial stereotactic radiotherapy poses several challenges for patient immobilization and tumor localization. Framed and frameless systems have been developed for this purpose. In 1995, Blomgren *et al.* described a technique of SBRT using a custom-made body cast and stereotactic coordinates (22). Lohr *et al.* introduced in 1999 a body cast and head mask system with a stereotactic body frame for patients with paraspinal tumors in the thoracic and lumbar spine, the same group treated also liver tumors with single dose stereotactic irradiation using a vacuum pillow and an abdominal compression. Both groups reported an acuracy of ≤5 mm (23,24). For the lung, Uematsu *et al.* introduced 2001 a frameless approach using the FOCAL unit, a combination of linac, kV simulation and a CT-scanner. Breathing with an oxygen mask and an abdominal compression belt allowed the intrafractional tumor motion to be less than 5 mm (25).

The growing interest in SBRT has been driven by advances in the radiotherapy planning imaging techniques and delivering techniques, which allow increasing treatment precision (26). A matter of concern by the use of SBRT technique in the treatment of lung tumors is their potential susceptibility to breathing-induced target movements, which might lead to dosimetric uncertainty and discrepancies between planned and delivered doses. This problem is a major concern for all tumor sites in the thorax (27). In 50% of lung tumors, a movement of 0.5 to 1 cm is observed, in 10% of more than 1 cm (28). While a broad spectrum of movement patterns is observed, by far the predominant direction of movements is longitudinally in the cranio- caudal direction (29). One solution of the breathing motion problem is the use of four-dimensional computed tomography (4D-CT) scans that correlate CT images with respiratory phases, allowing the visualization of the tumor motion (30). The concept of gating uses this information, and will enable radiation beam delivery only when the lung, and thus the target, are in a defined proportion of the breathing cycle (31).

Real-time target tracking (continuous adapting of the radiation beam to the tumor position) or positioning with a fully robotic patient positioning system with six degrees of freedom are methods used to reduce the treatment margins but are not widely clinically implemented (32-34).

Another approach is the use of the breath-hold and respiration-synchronized gating. A breath-hold technique using ABC© (Active Breathing Control, Elekta, Crawley, UK) has been shown to be an accurate and clinically useful tool. It has the advantage of reducing the target motion such that the gross tumor volume (GTV) resembles a primarily static tumor on the planning CT scan. Intra- and interfractional reproducibility of this system is 1.7 and 3.7 mm (35-37).

Clinical experience and toxicitys

One of the first SBRT trials for patients with medically inoperable NSCLC was the trial of the University of Indiana. The group recently updated the results of the phase II study. A total of 70 medically inoperable patients were included in the study. The SBRT treatment dose of 60-66 Gy was prescribed to the 80% isodose volume in three fractions. Median follow-up was 50.2 months and

Table 1 Summary of the results of the prospective trials of SBRT for NSCLC

Author [Year]	No. of patients	Dose	Median follow up	Outcomes
Fakiris *et al.* [2009]	70	T1: 3x20 Gy	50.2 months	3-year LC : 88.1%
Phase II		T2: 3x22 Gy		3-year OS 42.7%
		DP at 80%		3-year CSS: 81.7%
Baumann *et al.* [2009]	57	3x15 Gy	35 months	3-year LC: 92%
Phase II		DP at 65%		1-, 2-, 3-year OS: 86%, 65%, 60%
				1-, 2-, 3-year CSS: 93%, 88%, 88%
				3-year PFS: 52%
Timmerman *et al.* [2006]	70	3x20 Gy	17.5 months	2-year LC 95%
		3x22Gy		2-year OS 54.7%
Koto *et al.* [2007]	31	3x15 Gy	32 months	3-year LC: 77.9% (T1)
Phase II		8x7.5 Gy		3-year LC: 40% (T2)
		DP at 80%		3-year OS: 71.7%
				3-year CSS: 83.5%
Ricardi *et al.* [2010]	62	3x15 Gy	28 months	3-year LC: 87.8%
Phase II		DP at 80%		3-year OS: 57.1%
				3-year CSS: 83.5%
Timmerman *et al.* [2010]	55	3x18 Gy	34.4 months	3-year LC: 97.6 %
Phase II		DP at 80%		3-year OS: 55.8%

Abbbreviations: LC, local control; OS, overall survival: CSS, cancer specific survival; DP, dose prescription.

the local control at 3 years was 88.1%. Median survival was 32.4 months, the 3-year overall survival was 42.7% and the cancer-specific survival at 3 years was 81.7%. There was no difference in local control or survival between the T1 and T2 tumors, by tumor volume or by peripheral or central location. Grade 3 to 5 toxicity occurred in 5 of 48 patients with peripheral lung tumors (10.4%) and in 6 of 22 patients (27.3%) with central tumors (38).

The Scandinavian group also updated their results from a phase II trial. They treated 57 patients with NSCLC with SBRT with 15 Gy times three with a dose prescription at the 67% isodose of the planning target volume. Overall- and cancer-specific survival at 1, 2, and 3 years was 86%, 65%, 60%, and 93%, 88%, 88%, respectively. There was no statistically significant difference in survival between patients with T1 or T2 tumors, but the estimated risk of all failure (local, regional, or distant metastases) was increased in patients with T2 (41%) compared with those with T1 (18%) tumors. Local control at 3 years was 92%, local relapse was observed in four patients (7%) (39).

In 2006, Timmerman *et al.* reported the results of 70 patients treated with SBRT with a dose of 60 to 66 Gy total in three fractions during 1 to 2 weeks. The 3-month major response rate was 60%, the local control at 2 years was 95%. Median overall survival was 32.6 months and 2-year overall survival was 54.7%. Grade 3 to 5 toxicity occurred in a total of 14 patients. Among patients experiencing toxicity, the median time to observation was 10.5 months. Patients treated for tumors in the peripheral lung had 2-year freedom from severe toxicity of 83% compared with only 54% for patients with central tumors (40).

A group from Japan, reported their results of another phase II trial. They performed SBRT for 31 stage I NSCLC patients. SBRT was administered as 45 Gy in 3 fractions, however, when the tumor was close to an organ at risk, 60 Gy in 8 fractions were used. The doses were prescribed at the center of the tumors. The 3-year local control rates of T1 and T2 tumors were 77.9% and 40.0%, respectively. The 3-year overall and cause-specific survival rates were 71.7% and 83.5%, respectively. Five patients developed acute pulmonary toxicity ≥ grade 2 (41).

Ricardi *et al.* published in 2010 the final results of the phase II trial, where they included 62 patients with stage I NSCLC and treated them with three fractions of 15 Gy each, given every other day during a 1 week time, up to a total dose of 45 Gy. The dose was prescribed to the 80%-isodose encompassing planning target volume. At 3 years, local control rate was 87.8%, cancer-specific survival

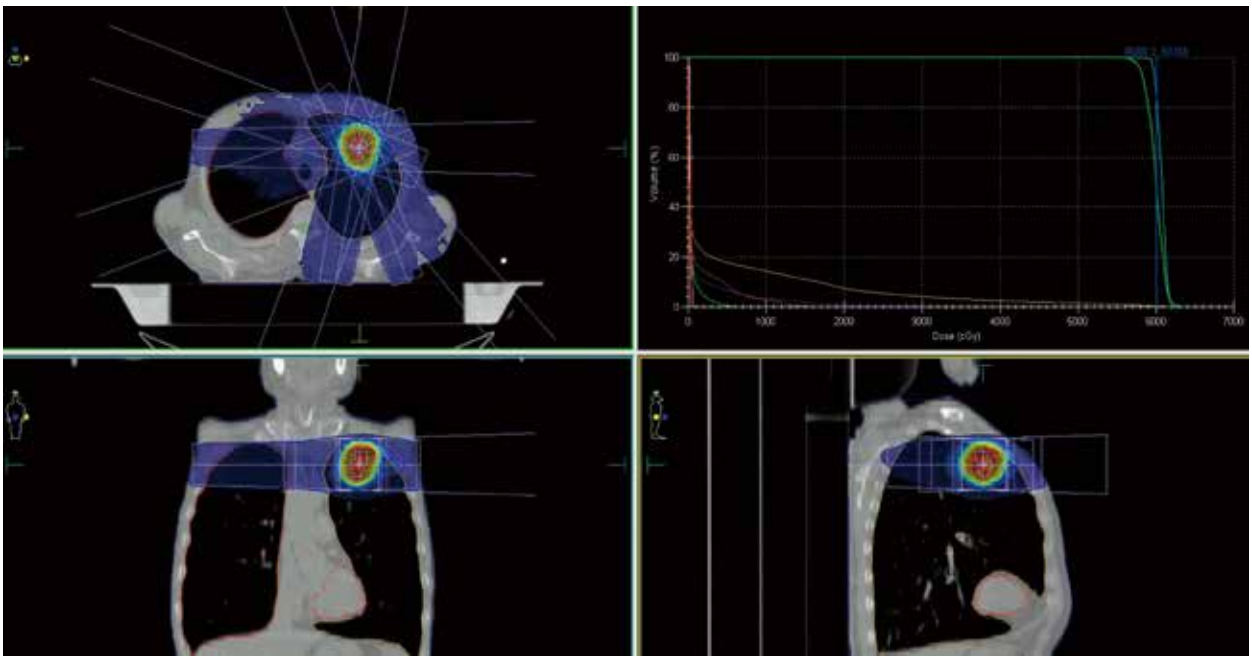


Figure 1 Dose distribution and DVH for one patient, treated with 5×12 Gy SBRT for lung metastases.

72.5%, overall survival 57.1%, the majority of patients did not experience any toxicity; mild skin reactions, fatigue, dyspnea/cough or transient thoracic pain were recorded in approximately 10% of patients (42).

Recently, Timmerman *et al.* published the results of the RTOG 0236 trial. A total of 59 patients accrued, of which 55 were evaluable (44 patients with T1 tumors and 11 patients with T2 tumors) with a median follow-up of 34.4 months. The 3 year primary tumor control rate was 97.6%, the 3-year rate of disseminated failure was 22.1%. The rates for disease-free survival and overall survival at 3 years were 48.3% and 55.8%, respectively. The median overall survival was 48.1 months. Protocol-specified treatment-related grade 3 adverse events were reported in 7 patients, grade 4 adverse events were reported in 2 patients. No grade 5 adverse events were reported (43). *Table 1* summarize the results of the prospective trials of the SBRT for patients with early stage NSCLC.

In a study, accomplished in our department, we included patients with 50 lung lesions who were treated with image-guided breath-hold SBRT with a regimen of 60 Gy in five fractions (*Figure 1*). Breath hold was performed with Active Breathing Control (ABC®, Elekta). Two year overall survival rate was more than 40%. 2-year local control rate was more than 80% without significant toxicity (44).

As shown above, the local control rates are more than 90%, when total doses from 54 to 60 Gy in three fractions are used. Currently, the RTOG 0915 trial is comparing two different SBRT fractionation schedules: 34 Gy in 1 fraction *vs.* 48 Gy in 4 fractions for patients with peripheral stage I NSCLC. The fractionation that proves to be less toxic, will be compared to the SBRT treatment schedule recommended by the RTOG (54 Gy in 3 fractions) in a phase III RTOG trial. The Dutch trial ROSEL (Radiosurgery Or Surgery for Early Lung cancer) will compare surgery and SBRT for patients with stage I NSCLC. Primary objectives of the trial will be the local and regional tumor control, quality of life and treatment costs of 2- and 5-years. A similar study is the STARS (Stereotactic Radiosugery *vs.* Surgery) trial, which is comparing surgery and radiosurgery with CyberKnife. Endpoint is the overall survival at 3 years.

High single doses radiation therapy of lung tumors is a special challenge because of diverse reasons such as the highly volume dependent radiosensitivity of the healthy lung tissue and surrounding organs at risk (oesophagus, heart), the breathing-induced motion of pulmonary targets and the dosimetrically difficult situation of a soft-tissue lesion surrounded by low-density lung tissue.

Besides the vital organs at risk heart and oesophagus, the lung itself is one of the most radiation-sensitive organs with two distinctive manifestations of radiation damage with different time frames. As a severe early (subacute) side effect of radiation therapy, pneumonitis occurs in 5-15% 4-6 weeks after conventionally fractionated large-volume

thoracic irradiation. Symptoms include dyspnoe upon activity, cough and subfebrile temperatures. The incidence of radiation pneumonitis depends on the radiation dose and the irradiated volume of the normal lung tissue (45). As a late side effect and consequence of radiation pneumonitis, pulmonary fibrosis may arise, rendering the affected tissue without function.

Tumor location is a well known predicting factor, which predicts severe toxicities, when using SBRT (54-60 Gy in 3 fractions) for patients with stage I NSCLC. Voroney *et al.* reported chest wall pain and rib fractures in patients with peripheral lung lesions (46). There is also a higher incidence of severe toxicities, when treating patients with 60 Gy in three fractions with central lung tumors, adjacent to mediastinal structures, defined as within 2 cm of the proximal bronchial tree, brachial plexus, or vertebral body. It seems, that in this cases, it is safer to apply the dose in more than 3 fractions (for example 12 times 5 Gy, 8 times 7. 5 or 60 Gy in 4-5 fractions) (40,47,48).

logical rationale

Over the last decades new insight into biological effects of irradiation in tissue has led to a paradigm change. The single target cell theory and solely cell kill from DNA damage is not sufficient to explain the complex biological effects of radiation. Furthermore, and specifically in SABR, the linear quadratic model-which is based on this rather simple theory and obtained from *in vitro* studies-may not be appropriate to assess *in vivo* data from SABR studies (49).

The importance of the tumor-microenvironment, the cross talk of malignant cells and host cells, the tumor bed effect, and the importance of other target cells than cancer cells are focus of intense ongoing research.

In addition, the radiobiology behind the effectiveness of high single doses or a small number of fractions of radiation may be very different from that underlying conventional fractionated non-ablative radiotherapy.

In this respect, endothelial cell apoptosis and micro-vascular dysfunction is observed only after high single doses of at least 8-10 Gy contributing significantly to tumor cell lethality and tumor cure by SABR (50-53). Although, the underlying mechanism of successive tissue damage and conversion of sub-lethal damage in tumor cells to lethal damage is not clear, it might involve leakage of circulating factors, a bystander effect of endothelial damage and ischemia induced complex cellular and molecular signalling.

In this respect, SABR might improve the elimination of potentially existent radio-resistant tumor stem cells which is a prerequisite for cancer cure. Tumor stem cells are thought to have better DNA repair mechanisms (54,55). In between fractions of conventional radiotherapy tumor (stem) cells try to repair sub-lethal damage, they can proliferate and transform into even more radio-resistant cells which possibly might facilitate tumor cell spread. After SABR and consequent micro-vascular dysfunction less repair and even direct apoptosis of cancer stem cells is conceivable. Ch'ang *et al.* observed stem cell apoptosis after single doses of 17Gy and higher (56).

In summary, endothelial cells and cancer stem cells may require a threshold dose to be crossed before their death is triggered which only can be accomplished by SABR.

Another aspect refers to radiation induced inflammatory and immune response. Radiation-induced inflammatory cytokine production is generally considerably stronger at higher radiation doses. It seems likely that dose fractionation may minimize the damage that results from this source by allowance of tissue repair.

Although likely to generate more inflammation, high local doses may be superior at generating "danger" signalling and rapid cell death and promoting anti-tumor immunity (57,58). Radiation induced massive tumor cell death by SABR leads to release of HMGB1 proteins among others from dying cells. Next to other proteins HMGB1 acts as a danger signal, a so called endogenous damage-associated molecular pattern (DAMP). Dying cells are phagocytosed by immature dendritic cells (DCs). DAMP signal through toll like receptors (TLR4 and TLR2) and are mandatory for host dendritic cells to mature (59). As a result antigen presenting cells (APCs) develop as targets for antigen specific CD8+ cells leading to a specific immune response.

As for apoptosis, it was shown that an immune response was optimal after doses of 8-10 Gy and higher.

Altogether, there are several biological aspects that might explain the excellent clinical tumor control rates after SABR.

Technical advancement

Accurate dose delivery to the patient is of utmost importance in external beam radiotherapy (EBRT) particularly if hypofractionated treatment techniques and/or dose escalation are used as in stereotactic body radiation therapy (SBRT). A precise dose calculation, delivery with steep dose gradients between tumor and healthy tissue and accurate tumor localization is essential.

In the last few years a lot of new methods and techniques were introduced in radiotherapy including intensity-modulated delivery (IMRT) with its steep dose gradients. IMRT offers the possibility to shape the dose distribution

Figure 2 Planning CT (purple) matched on the Cone Beam CT (green) of one patient treated with SBRT for single lung metastasis.

exactly around the target structures while organs at risk (OAR) are mostly spared. The full potential of IMRT can only be used when safety margins around the targets are reduced.

Image-guided radiotherapy (IGRT) offers the potential to reduce planning margins due to exact patient positioning and thus further helps to increase the therapeutic window (60-62). It has become clinical practice to re-position the patient according to 3D imaging data. To detect internal misalignment of organs relatively to the bony structures, it is preferable to use an image guidance system which is able to discriminate soft tissues. The common systems which can be used for online position correction are CT-on-rails (63), conebeam CT (CBCT) (*Figure 2*) (64-66), ultrasound (67,68) or electromagnetic signals (69). The positive effects of IGRT on the therapeutic dose distribution and the additional imaging dose have already been analysed (70-72).

An exact image guided (or stereotactic) positioning of the patient is rather easy to achieve in rigid structures such as the skull but is a major challenge for mobile organs. Tumors in the thorax and abdomen can move significantly with respiration. This has to be taken into account during the treatment planning process and treatment delivery (73). Several approaches use four-dimensional (4D) CT- or CBCT-datasets, that allow the determination of tumor position in different breathing phases (74-76). However, sometimes the increased time for processing the large amount of data and also the extended and more complex workflow limit the usability in clinical routine (62,74). In contrast to those approaches breathhold techniques (77) have been suggested to reduce the effect of breathing motions while maintaining tight PTV margins around the tumor. With inspiration-breathhold treatment techniques ITV and thus PTV margins can potentially be reduced and doses can be escalated resulting in better tumor control rates. In addition, the total irradiated lung volume and, importantly, lung mass can be kept to a minimum (77-80).

Up to now long image acquisition times of ~60-120 s (kV-CBCT) limit the number of patients who can undergo volume image guidance under breathhold to eliminate motion artefacts. Therefore a new approach was suggested to combine the kV and the MV source of the linac for a simultaneously acquired, fast (~15 s) and accurate kVMV-CBCT reconstruction for image guided patient positioning. kVMV-CBCT based on a standard linac is promising and can provide ultra-fast online volume image guidance with low imaging dose and sufficient image quality for fast and accurate patient positioning for patients with lung cancer under breathhold (81,82).

Conclusions

Highly conformal body-stereotactic treatment with only a

few or even single fractions has been successfully applied to extracranial lesions such as lung tumors, achieving high local control rates of more than 90% (97-98% at 3 years). The recommended from the RTOG fractionation schedule of 3 times 18 Gy, can be safely applied, whereby in patients with central tumors it is recommended to use more than 3 fractions (for example 5×12 Gy) to avoid severe toxicities. Additionally, despite comorbidities, SBRT is well tolerated even in patients with lower performance status, due to the less number of fractions (3 to 5). Breathhold techniques can help to reduce the effect of breathing motions while maintaining tight PTV margins around the tumor. During imaging they help to hold the tumor in a quasi stable position and thus reduces motion artefacts to a minimum. However, Long image acquisition times of currently ~60-120 s limit the number of patients who can be imaged with standard on board kV-CBCT for patient positioning at the linac during one breathhold phase. With the implementation combined kVMV-CBCT in the future, a shortening of the imaging time to ~15 s can be expected.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212-36.
2. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351-60.
3. Kupelian PA, Komaki R, Allen P. Prognostic factors in the treatment of node-negative nonsmall cell lung carcinoma with radiotherapy alone. Int J Radiat Oncol Biol Phys 1996;36:607-13.
4. Sibley GS, Jamieson TA, Marks LB, et al. Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: the Duke experience. Int J Radiat Oncol Biol Phys 1998;40:149-54.
5. Fernandes AT, Shen J, Finlay J, et al. Elective nodal irradiation (ENI) vs. involved field radiotherapy (IFRT) for locally advanced non-small cell lung cancer (NSCLC): A comparative analysis of toxicities and clinical outcomes. Radiother Oncol 2010;95:178-84.
6. Slotman BJ, Antonisse IE, Njo KH. Limited field irradiation in early stage (T1-2N0) non-small cell lung cancer. Radiother Oncol 1996;41:41-4.
7. Sulman EP, Komaki R, Klopp AH, et al. Exclusion of elective nodal irradiation is associated with minimal elective nodal failure in non-small cell lung cancer. Radiat Oncol 2009;4:5.
8. Krol AD, Aussems P, Noordijk EM, et al. Local irradiation alone for peripheral stage I lung cancer: could we omit the elective regional nodal irradiation? Int J Radiat Oncol Biol Phys 1996;34:297-302.
9. Blomgren H, Lax I, Näslund I, et al. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 1995;34:861-70.
10. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 2003;124:1946-55.
11. Fowler JF, Tomé WA, Fenwick JD, et al. A challenge to traditional radiation oncology. Int J Radiat Oncol Biol Phys 2004;60:1241-56.
12. Hof H, Herfarth KK, Münter M, et al. Stereotactic single-dose radiotherapy of stage I non-small-cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 2003;56:335-41.
13. Uematsu M, Shioda A, Tahara K, et al. Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience. Cancer 1998;82:1062-70.
14. Li B, Yu J, Suntharalingam M, et al. Comparison of three treatment options for single brain metastasis from lung cancer. Int J Cancer 2000;90:37-45.
15. Rades D, Pluemer A, Veninga T, et al. Whole-brain radiotherapy versus stereotactic radiosurgery for patients in recursive partitioning analysis classes 1 and 2 with 1 to 3 brain metastases. Cancer 2007;110:2285-92.
16. Wang LG, Guo Y, Zhang X, et al. Brain metastasis: experience of the Xi-Jing hospital. Stereotact Funct Neurosurg 2002;78:70-83.
17. Papiez L, Timmerman R. Hypofractionation in radiation therapy and its impact. Med Phys 2008;35:112-8.
18. de Pooter JA, Méndez Romero A, Jansen WP, et al. Computer optimization of noncoplanar beam setups improves stereotactic treatment of liver tumors. Int J Radiat Oncol Biol Phys 2006;66:913-22.
19. de Pooter JA, Méndez Romero A, Wunderink W, et al. Automated non-coplanar beam direction optimization improves IMRT in SBRT of liver metastasis. Radiother Oncol 2008;88:376-81.
20. Liu R, Buatti JM, Howes TL, et al. Optimal number of beams for stereotactic body radiotherapy of lung and liver

lesions. Int J Radiat Oncol Biol Phys 2006;66:906-12.
21. Chang BK, Timmerman RD. Stereotactic body radiation therapy: a comprehensive review. Am J Clin Oncol 2007;30:637-44.
22. Blomgren H, Lax I, Näslund I, et al. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 1995;34:861-70.
23. Lohr F, Debus J, Frank C, et al. Noninvasive patient fixation for extracranial stereotactic radiotherapy. Int J Radiat Oncol Biol Phys 1999;45:521-7.
24. Herfarth KK, Debus J, Lohr F, et al. Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial. J Clin Oncol 2001;19:164-70.
25. Uematsu M, Shioda A, Suda A, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. Int J Radiat Oncol Biol Phys 2001;51:666-70.
26. Haasbeek CJ, Slotman BJ, Senan S. Radiotherapy for lung cancer: clinical impact of recent technical advances. Lung Cancer 2009;64:1-8.
27. Gui M, Feng Y, Yi B, et al. Four-dimensional intensity-modulated radiation therapy planning for dynamic tracking using a direct aperture deformation (DAD) method. Med Phys 2010;37:1966-75.
28. Liu HH, Balter P, Tutt T, et al. Assessing Respiration-Induced Tumor Motion and Internal Target Volume Using Four-Dimensional Computed Tomography for Radiotherapy of Lung Cancer. Int J Radiat Oncol Biol Phys 2007;68:531-40.
29. Seppenwoolde Y, Shirato H, Kitamura K, et al. Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. Int J Radiat Oncol Biol Phys 2002;53:822-34.
30. Keall P. 4-dimensional computed tomography imaging and treatment planning. Semin Radiat Oncol 2004;14:81-90.
31. Briere TM, Beddar S, Balter P, et al. Respiratory gating with EPID-based verification: the MDACC experience. Phys Med Biol 2009;54:3379-91.
32. Hoisak JD, Sixel KE, Tirona R, et al. Correlation of lung tumor motion with external surrogate indicators of respiration. Int J Radiat Oncol Biol Phys 2004;60:1298-306.
33. Keall PJ, Cattell H, Pokhrel D, et al. Geometric accuracy of a real-time target tracking system with dynamic multileaf collimator tracking system. Int J Radiat Oncol Biol Phys 2006;65:1579-84.
34. Guckenberger M, Meyer J, Wilbert J, et al. Precision of image-guided radiotherapy (IGRT) in six degrees of freedom and limitations in clinical practice. Strahlenth Onkol 2007;183:307-13.
35. Boda-Heggemann J, Fleckenstein J, Lohr F, et al. Multiple breath-hold CBCT for online image guided radiotherapy of lung tumors: simulation with a dynamic phantom and first patient data. Radiother Oncol 2011;98:309-16.
36. Dawson LA, Eccles C, Bissonnette JP, et al. Accuracy of daily image guidance for hypofractionated liver radiotherapy with active breathing control. Int J Radiat Oncol Biol Phys 2005;62:1247-52.
37. Panakis N, McNair HA, Christian JA, et al. Defining the margins in the radical radiotherapy of non-small cell lung cancer (NSCLC) with active breathing control (ABC) and the effect on physical lung parameters. Raiother Oncol 2008;87:65-73.
38. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75:677-82.
39. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.
40. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
41. Koto M, Takai Y, Ogawa Y, et al. A phase II study on stereotactic body radiotherapy for stage I non-small cell lung cancer. Radiother Oncol 2007;85:429-34.
42. Ricardi U, Filippi AR, Guarneri A, et al. Stereotactic body radiation therapy for early stage non-small cell lung cancer: results of a prospective trial. Lung Cancer 2010;68:72-7.
43. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
44. Boda-Heggemann J, Lohr F, Wertz H, et al. Repeat ABC breath- hold Imaging With Cone-beam CT. ASTRO 2011 Abstract 2010.
45. De Neve W, De Wagter C. Lethal pneumonitis in a phase I study of chemotherapy and IMRT for NSCLC: the need to investigate the accuracy of dose computation. Radiother Oncol 2005;75:246-7.
46. Voroney JP, Hope A, Dahele MR, et al. Chest wall pain and rib fracture after stereotactic radiotherapy for peripheral non-small cell lung cancer. J Thorac Oncol 2009;4:1035-7.
47. Song SY, Choi W, Shin SS, et al. Fractionated stereotactic

body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. Lung Cancer 2009;66:89-93.
48. Guckenberger M, Heilman K, Wulf J, et al. Pulmonary injury and tumor response after stereotactic body radiotherapy (SBRT): results of a serial follow-up CT study. Radiother Oncol 2007;85:435-42.
49. Kirkpatrick JP, Meyer JJ, Marks LB. The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery. Semin Radiat Oncol 2008;18:240-3.
50. Garcia-Barros M, Paris F, Cordon-Cardo C, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science 2003;300:1155-9.
51. Fuks Z, Kolesnick R. Engaging the vascular component of the tumor response. Cancer Cell 2005;8:89-91.
52. Paris F, Fuks Z, Kang A, et al. Endothelial apoptosis as the primary lesion initiating intestinal radiation damage in mice. Science 2001;293:293-7.
53. Truman JP, García-Barros M, Kaag M, et al. Endothelial membrane remodeling is obligate for anti-angiogenic radiosensitization during tumor radiosurgery. PLoS One 2010;5:e12310.
54. Bao S, Wu Q, McLendon RE , et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature 2006;444:756-60.
55. Al-Hajj M, Wicha MS, Benito-Hernandez A, et al. Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA 2003;100:3983-8.
56. Ch'ang HJ, Maj JG, Paris F, et al. ATM regulates target switching to escalating doses of radiation in the intestines. Nat Med 2005;11:484-90.
57. McBride WH, Chiang CS, Olson JL, et al. A sense of danger from radiation. Radiat Res 2004;162:1-19.
58. Demaria S, Formenti SC. Sensors of ionizing radiation effects on the immunological microenvironment of cancer. Int J Radiat Biol 2007;83:819-25.
59. Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 2007;13:1050-9.
60. Yeung AR, Li JG, Shi W, et al. Tumor localization using cone-beam CT reduces setup margins in conventionally fractionated radiotherapy for lung tumors. Int J Radiat Oncol Biol Phys 2009;74:1100-7.
61. Boda-Heggemann J, Lohr F, Wenz F, et al. kV cone-beam CT-based IGRT: a clinical review. Strahlenther Onkol 2011;187:284-91.
62. Wang L, Feigenberg S, Chen L, et al. Benefit of three-dimensional image-guided stereotactic localization in the hypofractionated treatment of lung cancer. Int J Radiat Oncol Biol Phys 2006;66:738-47.
63. Oita M, Takegawa Y, Yagi H, et al. Quality control (QC) of CT on rail system (FOCAL Unit) with a micro-multi leaf collimator (mMLC) using new GafChromic film for stereotactic radiotherapy. Nihon Hoshasen Gijutsu Gakkai Zasshi 2006;62:711-3.
64. Amer A, Marchant T, Sykes J, et al. Imaging doses from the Elekta Synergy X-ray cone beam CT system. Br J Radiol 2007;80:476-82.
65. Roxby P, Kron T, Foroudi F, et al. Simple methods to reduce patient dose in a Varian cone beam CT system for delivery verification in pelvic radiotherapy. Br J Radiol 2009;82:855-9.
66. Groh BA, Siewerdsen JH, Drake DG, et al. A performance comparison of flat-panel imager-based MV and kV cone-beam CT. Med Phys 2002;29:967-75.
67. Fuss M, Salter BJ, Cavanaugh SX, et al. Daily ultrasound-based image-guided targeting for radiotherapy of upper abdominal malignancies. Int J Radiat Oncol Biol Phys 2004;59:1245-56.
68. Boda-Heggemann J, Mennemeyer P, Wertz H, et al. Accuracy of ultrasound-based image guidance for daily positioning of the upper abdomen: an online comparison with cone beam CT. Int J Radiat Oncol Biol Phys 2009;74:892-7.
69. Kupelian P, Willoughby T, Mahadevan A, et al. Multi-institutional clinical experience with the Calypso System in localization and continuous, real-time monitoring of the prostate gland during external radiotherapy. Int J Radiat Oncol Biol Phys 2007;67:1088-98.
70. Wertz H, Lohr F, Dobler B, et al. Dosimetric consequences of a translational isocenter correction based on image guidance for intensity modulated radiotherapy (IMRT) of the prostate. Phys Med Biol 2007;52:5655-65.
71. Wertz H, Lohr F, Dobler B, et al. Dosimetric impact of image-guided translational isocenter correction for 3-D conformal radiotherapy of the prostate. Strahlenther Onkol 2007;183:203-10.
72. Walter C, Boda-Heggemann J, Wertz H, et al. *In vivo* dose measurements of extra dose from cone-beam computed tomography. Int J Radiat Oncol Biol Phys 2006;66:632.
73. Juhler Nøttrup T, Korreman SS, Pedersen AN, et al. Intra- and interfraction breathing variations during curative radiotherapy for lung cancer. Radiother Oncol 2007;84:40-8.
74. Rietzel E, Pan T, Chen GT. Four-dimensional computed tomography: image formation and clinical protocol. Med Phys 2005;32:874-89.
75. Sonke JJ, Rossi M, Wolthaus J, et al. Frameless stereotactic body radiotherapy for lung cancer using four-dimensional

cone beam CT guidance. Int J Radiat Oncol Biol Phys 2009;74:567-74.
76. Underberg RW, Lagerwaard FJ, Slotman BJ, et al. Benefit of respiration-gated stereotactic radiotherapy for stage I lung cancer: an analysis of 4DCT datasets. Int J Radiat Oncol Biol Phys 2005;62:554-60.
77. Barnes EA, Murray BR, Robinson DM, et al. Dosimetric evaluation of lung tumor immobilization using breath hold at deep inspiration. Int J Radiat Oncol Biol Phys 2001;50:1091-8.
78. Kashani R, Balter JM, Hayman JA, et al. Short-term and long-term reproducibility of lung tumor position using active breathing control (ABC). Int J Radiat Oncol Biol Phys 2006;65:1553-9.
79. Partridge M, Tree A, Brock J, et al. Improvement in tumour control probability with active breathing control and dose escalation: a modelling study. Radiother Oncol 2009;91:325-9.
80. Thompson BP, Hugo GD. Quality and accuracy of cone beam computed tomography gated by active breathing control. Med Phys 2008;35:5595-608.
81. Blessing M, Stsepankou D, Wertz H, et al. Breath-hold target localization with simultaneous kilovoltage/megavoltage cone-beam computed tomography and fast reconstruction. Int J Radiat Oncol Biol Phys 2010;78:1219-26.
82. Wertz H, Stsepankou D, Blessing M, et al. Fast kilovoltage/megavoltage (kVMV) breathhold cone-beam CT for image-guided radiotherapy of lung cancer. Phys Med Biol 2010;55:4203-17.

Cite this article as: Simeonova AO, Fleckenstein K, Wertz HJ, Frauenfeld A, Boda-Heggemann J, Lohr F, Wenz F. Are three doses of stereotactic ablative radiotherapy (SABR) more effective than 30 doses of conventional radiotherapy? Transl Lung Cancer Res 2012;1:45-53. doi: 10.3978/j.issn.2218-6751.10.01

Controversy and Debate

Stereotactic ablative radiotherapy for stage I NSCLC: Successes and existing challenges

Joe Y. Chang

Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Correspondence to: Joe Y. Chang, MD, PhD, Clinical Section Chief and Director of Stereotactic Ablative Radiotherapy Program, Thoracic Radiation Oncology; Department of Radiation Oncology, Unit 97, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA, Email: jychang@mdanderson.org.

Submitted Jun 12, 2011. Accepted for publication Jun 13, 2011.
doi: 10.3978/j.issn.2072-1439.2011.06.02
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2011.06.02

Stereotactic ablative radiotherapy (SABR) has emerged as a standard treatment of peripherally located medically inoperable stage I non-small cell lung cancer (NSCLC) (1-5). With SABR, local control of primary tumors is greater than 90% in tumors up to 5 cm, and regional lymph node recurrence within the chest is low (5% to 10%). Distant metastasis remains a dominant pattern of failure (10% to 20%). SABR has been accepted by the National Comprehensive Cancer Network (NCCN) and is included in the NCCN treatment guidelines, and SABR is widely used (>75%) by radiation oncology centers, including community hospitals, according to a recent survey by the American Society for Radiation Oncology (ASTRO).

In this issue of the Journal of Thoracic Disease, Dr. Senan and colleagues reviewed the recent developments and controversies in SABR (6). Published data have consistently shown that SABR, when given at a biologically effective dose (BED) of greater than 100 Gy, achieves excellent local control with minimal toxicity, which is a significant improvement compared with conventional fractionated radiotherapy in stage I NSCLC (1-5). The dramatic improvement in local control could be due to the efficient killing of both radiosensitive and resistant cancer cells by ablative dose. Local control appears to depend on dose delivered and tumor size (1-5). As Dr. Senan and colleagues discussed, the dose delivered to the planning target volume (PTV) and isocenter can vary dramatically, depending on where the dose is prescribed (6). For example, a dose of 60 Gy prescribed to 60% of the isodose line could deliver 100 Gy to isocenter, and a dose of 60 Gy prescribed to isocenter could deliver only 57 Gy or even less to the PTV, depending on the location of the PTV. In addition, dose calculation algorithms used by treatment planning systems, such as pencil beam versus Monte Carlo calculation, can also cause dose variation (up to 15%). Therefore, it is very important to make sure that the PTV receives minimal dose coverage (the recommended BED is 100 Gy). To avoid missing the target and overdosing surrounding critical structures, image guidance (particularly volumetric image guidance) for each treatment and motion management in select cases with tumor motion greater than 1 cm are highly recommended (7).

SABR is a double-edged sword that can kill cancer cells but can also damage surrounding critical structures (2). Therefore, well-designed SABR requires a sharp dose gradient from ablative dose to tolerable dose. In addition, case selection and appropriate SABR dose regimens based on target location are crucial to reduce toxicity. Critical structures such as the esophagus, bronchial tree, spinal cord, brachial plexus, and trachea should not receive the ablative dose. Therefore, hilar lymph nodes and mediastinal lymph nodes should not be treated with SABR owing to their proximity to these critical structures. For lung parenchyma lesions close to these critical structures, individualized treatment planning for dose distribution (4) and/or reduced dose fraction size should be considered (8). Dr. Lagerwaard and colleagues proposed adaptive dose regimens that appeared to achieve promising outcomes (8). Dr. Xia and colleagues reported that 70 Gy prescribed to the gross tumor volume (GTV) in 10 fractions was tolerable in central lesions (9). Using 50 Gy in 4 fractions, we tailored the dose distribution to deliver the conformal dose to the target and avoid delivering the ablative dose to surrounding critical

structures using 4-dimensional computed tomography (CT)-based SABR panning, individualized dose-distribution techniques, and on-board volumetric (cone-beam CT or CT on rails) image verification for each fraction in central lesions, promising local control and acceptable toxicity would be achieved (4). For recurrent or new primary isolated lung parenchyma disease (< 4 cm) in patients who received prior conventional fractionated radiotherapy to chest, SABR achieved excellent local control (>90%), although toxicity was higher than patients who never received prior radiotherapy to chest but could be predicted using a clinical index model (10,11).

The role of SABR in patients without a pathologically confirmed diagnosis remains debatable. In most centers in the United States, SABR is not considered if there is no pathological confirmation for suspected new primary stage I NSCLC. However, Dr. Senan and colleagues note that the false-positive rate is less than 4.5% in The Netherlands, and they feel that SABR is justified in select cases without pathological confirmation when the false-positive rate is low. Treating physicians need to know the false-positive rate with clinical diagnosis in their region and discusstreatment options with their patients before considering SABR without pathological confirmation.

The rate of lymph node recurrence after SABR is between 5% and 10%, although these lymph nodes were not treated. This incidence rate is comparable with the rate of recurrence in surgical resection. The modern staging workup, including positron-emission tomography (PET)/CT, endobronchial ultrasound (EBUS), and mediastinoscopy has helped to stage these lymph nodes more accurately, and available data support treating the primary lesion only, particularly for small lesions located peripherally.

Follow-up images after SABR remain controversial owing to abnormal consolidation of lung parenchyma after SABR and residual PET activity. However, recent post-SABR PET images showed the predictive role of PET for local and regional recurrence and distant metastasis (12). A high post-SABR standardized uptake value (SUV) (>5) more than 3 months after SABR should raise suspicion for local recurrence and close follow-up is indicated. If the SUV remains high with serial images, biopsy should be considered to confirm the local recurrence (12).

The role of SABR in operable stage I NSCLC is promising, based on published data and SABR is being investigated in ongoing phase III clinical studies. In addition, distant metastasis remains a dominate pattern of failure in this group of patients after SABR, and clinical studies for adjuvant chemotherapy and for target treatment are ongoing. The identification of a molecular marker to predict distant metastasis would help clinicians decide which patients need adjuvant systemic treatment.

References

1. Onishi H, Araki T, Shirato H, Nagata Y, Hiraoka M, Gomi K, et al. Stereotactic hypofractionated high-dose irradiation for stage I non-small cell lung carcinoma clinical outcome in 245 subjects in a Japanese multi-institutional study. Cancer 2004;101:1623-31.
2. Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
3. Nagata Y, Takayama K, Matsuo Y, Norihisa Y, Mizowaki T, Sakamoto T, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiation therapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys 2005;63:1427-31.
4. Chang JY, Balter PA, Dong L, Yang Q, Liao Z, Jeter M, et al. Stereotactic body radiation therapy in centrally and superiorly located Stage I or isolated recurrent non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;72:967-71.
5. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
6. Senan S, Palma DA, Lagerwaard FJ. Stereotactic ablative radiotherapy for stage I NSCLC: Recent advances and controversies. J Thorac Dis 2011;3:189-96.
7. Chang JY, Dong L, Liu H, Starkschall G, Balter P, Mohan R, et al. Image-guided radiation therapy for non-small cell lung cancer. J Thorac Oncol 2008;3:177-86.
8. Lagerwaard FJ, Haasbeek CJA, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2008;70:685-92.
9. Xia T, Li H, Sun Q, Wang Y, Fan N, Yu Y, et al. Promising clinical outcome of stereotactic body radiation therapy for patients with inoperable Stage I/II non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006;66:117-25.
10. Kelly P, Balter PA, Rebueno N, Sharp HJ, Liao Z, Komaki R, et al. Stereotactic body radiation therapy for patients

with lung cancer previously treated with thoracic radiation. Int J Radiat Oncol Biol Phys 2010;78:1387-93.
11. Liu H, Zhang X, Vinogradskiy Y, Swisher SG, Komaki R, Chang JY. Predicting radiation pneumonitis after stereotactic ablative radiotherapy in patients previously treated with conventional thoracic radiotherapy. Int J Radiat Oncol Biol Phys. Forthcoming.
12. Zhang X, Balter P, Pan T, Allen P, Chuang H, Chang JY. PET/CT and outcome in lung cancer treated with stereotactic body radiation therapy. Int J Rad Onc Bio Phy 2010;s78: 16.

Cite this article as: Chang JY. Stereotactic ablative radiotherapy for stage I NSCLC: Successes and existing challenges. J Thorac Dis 2011;3(3):144-146. doi: 10.3978/j.issn.2072-1439.2011.06.02

Controversy and Debate

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

Gonzalo Varela, María Teresa Gómez-Hernández

Thoracic Surgery Service, Salamanca University Hospital and Salamanca's Bio-sanitary Institute (IBSAL), Salamanca, Spain

Correspondence to: Dr. Gonzalo Varela. Cirugía Torácica, Hospital Universitario, Paseo de San Vicente 58, 37007 Salamanca, Spain. Email: gvs@usal.es.

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 that 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 were 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 FEDG-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 in 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 were 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 were 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.

References

1. 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.
2. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 2013;24:1543-8.
3. D'Cunha J, Herndon JE 2nd, Herzan DL, et al. Poor correspondence between clinical and pathologic staging in stage 1 non-small cell lung cancer: results from CALGB 9761, a prospective trial. Lung Cancer 2005;48:241-6.
4. Shingyoji M, Nakajima T, Yoshino M, et al. Endobronchial ultrasonography for positron emission tomography and computed tomography-negative lymph node staging in non-small cell lung cancer. Ann Thorac Surg 2014;98:1762-7.
5. Whitson BA, Groth SS, Maddaus MA. Surgical assessment and intraoperative management of mediastinal lymph nodes in non-small cell lung cancer. Ann Thorac Surg 2007;84:1059-65.
6. Ricardi U, Frezza G, Filippi AR, et al. Stereotactic Ablative Radiotherapy for stage I histologically proven non-small cell lung cancer: an Italian multicenter observational study. Lung Cancer 2014;84:248-53.
7. European Society of Thoracic Surgeons Database Committee. Database Annual Report 2015. Available online: http://www.ests.org/_userfiles/pages/files/ESTS%20201Silver_Book_FULL_PEF.pdf, accessed on Aug 30th, 2015.
8. Yim AP, Wan S, Lee TW, et al. VATS lobectomy reduces cytokine responses compared with conventional surgery. Ann Thorac Surg 2000;70:243-7.
9. Falcoz PE, Puyraveau M, Thomas PA, et al. Video-assisted thoracoscopic surgery versus open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. Eur J Cardiothorac Surg 2016;49:602-9.
10. Higuchi M, Yaginuma H, Yonechi A, et al. Long-term

outcomes after video-assisted thoracic surgery (VATS) lobectomy versus lobectomy via open thoracotomy for clinical stage IA non-small cell lung cancer. J Cardiothorac Surg 2014;9:88.
11. Yan TD, Black D, Bannon PG, et al. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. J Clin Oncol 2009;27:2553-62.
12. Novoa N, Ballesteros E, Jiménez MF, et al. Chest physiotherapy revisited: evaluation of its influence on the pulmonary morbidity after pulmonary resection. Eur J Cardiothorac Surg 2011;40:130-4.
13. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol 2010;28:928-35.
14. Lanni TB Jr, Grills IS, Kestin LL, et al. Stereotactic radiotherapy reduces treatment cost while improving overall survival and local control over standard fractionated radiation therapy for medically inoperable non-small-cell lung cancer. Am J Clin Oncol 2011;34:494-8.
15. Brunelli A, Kim AW, Berger KI, et al. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e166S-90S.
16. Powell HA, Baldwin DR. Multidisciplinary team management in thoracic oncology: more than just a concept? Eur Respir J 2014;43:1776-86.
17. Novoa N, Jiménez MF, Aranda JL, et al. Effect of implementing the European guidelines for functional evaluation before lung resection on cardiorespiratory morbidity and 30-day mortality in lung cancer patients: a case-control study on a matched series of patients. Eur J Cardiothorac Surg 2014;45:e89-93; discussion e93.

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

Controversy and Debate

Improved survival with stereotactic ablative radiotherapy (SABR) over lobectomy for early stage non-small cell lung cancer (NSCLC): addressing the fallout of disruptive randomized data

Chad G. Rusthoven, Brian D. Kavanagh, Sana D. Karam

Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO 80045, USA

Correspondence to: Chad Rusthoven, MD. Department of Radiation Oncology, University of Colorado School of Medicine, 1665 N. Aurora Court, Suite 1032, Mail Stop F706, Aurora, CO 80045, USA. Email: chad.rusthoven@ucdenver.edu.

Abstract: The gold-standard therapy for early stage non-small cell lung cancer (esNSCLC) has historically been lobectomy with mediastinal lymph node dissection. However, up to one-third of patients with esNSCLC are considered medically-inoperable due to factors such as advanced age and comorbid illnesses. The past decade has witnessed a dramatic increase in the use of high-dose conformal radiotherapy delivered over 1-5 fractions, synonymously termed stereotactic ablative radiotherapy (SABR) or stereotactic body radiation therapy (SBRT). High rates of tumor control and favorable toxicity profiles have led to the adoption of SABR as the treatment of choice for medically-inoperable patients. Limited but growing data exist using SABR for medically-operable patients who are also candidates for lobectomy. A recent pooled analysis of two multicenter prospective randomized trials, the STARS (NCT00840749) and ROSEL (NCT00687986) protocols, published by Chang and colleagues (PMID 25981812) reported improved overall survival (OS) and reduced toxicity with SABR over lobectomy for medically-operable patients with esNSCLC. In this article we review the outcomes of this analysis in the context of existing radiotherapy and surgical data for NSCLC. Further, we discuss the potential causes and implications of these provocative results, including the shifting balance between oncologic control and treatment-related mortality in comparisons of SABR and surgical resection, termed the Head Start Effect.

Keywords: Stereotactic ablative radiation (SABR); stereotactic body radiation therapy (SBRT); lobectomy; surgery; non-small cell lung cancer (NSCLC); randomized trial; phase III; head start effect

Submitted Jun 09, 2015. Accepted for publication Jun 12, 2015.
doi: 10.3978/j.issn.2305-5839.2015.06.15
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.06.15

A recent report by Chang *et al*. presented a pooled analysis of data from two prospective multicenter randomized trials, the STARS (NCT00840749) and ROSEL (NCT00687986) protocols, comparing lobectomy and stereotactic ablative radiotherapy (SABR) for medically operable patients with T1-2a (<4 cm) N0 M0 non-small cell lung cancer (NSCLC) (1). The results of this analysis were provocative, demonstrating an absolute improvement in overall survival (OS) of 16% at 3 years (95% *vs*. 79%, P=0.037) and a decrease in grade ≥3 toxicity (10% *vs*. 48%) in favor of SABR. The primary limitations of this analysis are related to the small patient numbers available from the two trials (58 total patients; 31 treated with SABR and 27 with surgery), which were both closed early following poor accrual. In their discussion, the authors suggest that their results establish a state of equipoise regarding the optimal management for patients with operable early-stage NSCLC (esNSCLC) and should galvanize recruitment to subsequent randomized trials. In the meantime, the foundation of lobectomy as the unassailable gold-standard approach for operable esNSCLC has, for the first time, been shaken by contradictory randomized data.

Reconciliation of the results of the Chang paper with the historic outcomes for esNSCLC requires some familiarity with the literature on SABR for esNSCLC. First, a critical distinction must be made between the prognosis

Table 1 Comparison of Chang *et al.* (1) data with SABR results for medically-operable patients with esNSCLC

Study	N	Eligible	Treatment	Age	Median follow-up (months)	Local or lobar failure	Regional failures	Distant failures	PFS	OS	Toxicity
Chang (1), Lobectomy Cohort Phase III	27	Operable T1-2a N0	Lobectomy	67	35.4	3-year 0%	3-year 4%	3-year 9%	3-year 80%	3-year 79%	Grade ≥3 (48%) 1 Grade 5
Chang (1), SABR Cohort Phase III	31	Operable T1-2a N0	54 Gy (3 fractions); 50 Gy (3 fractions); 60 Gy (3 fractions)	67	40.2	3-year 4%	3-year 10%	3-year 3%	3-year 86%	3-year 95%	Grade 3 (10%)
Timmerman (6), RTOG 0618 Phase II	26	Operable T1-2 N0	54 Gy (3 fractions)	72	25	2-year 20%	2-year 12%	2-year 15%	2-year 65%	2-year 84%	Grade 3 (16%)
Lagerwaard (7), Retrospective	177	Operable T1-T2 N0	60 Gy (risk-adapted to 3, 5, or 8 fractions)	76	31.5	3-year 7%	3-year 10%	3-year 10%	3-year 81%	3-year 85%	Grade ≥3 pneumonitis in 2% and rib fracture 3%
Onishi (8), Retrospective	87	Operable T1-2 N0	45-72.5 Gy at isocenter (3-10 fractions)	74	55	5-year 13%	5-year 15%	5-year 25%	NR	5-year 70%	Grade 3 (8.2%)

SABR, stereotactic ablative radiotherapy; esNSCLC, early stage non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; NR, not reported.

of medically-operable patients in the Chang study and medically-inoperable patients, with the latter representing the majority of patients treated with SABR in reported series to date (2,3). Operable patients are, by definition, those with adequate physiologic reserve to undergo surgery, while inoperable patients are those exceeding acceptable risk thresholds for operative mortality due to factors such as advanced age, pulmonary function, cardiovascular fitness, and performance status (4). Baseline prognostic differences for operable and inoperable patients, irrespective of therapy, are highlighted by a study of 257 esNSCLC patients uniformly treated with SABR, where the 5-year survival rates were 65% *vs.* 35% (P<0.001) for medically-operable and inoperable patients, respectively (5). These substantial prognostic disparities render survival comparisons between operable patients treated with one modality (e.g., lobectomy) and inoperable patients treated with another modality (e.g., SABR or sublobar resection) inappropriate and confound the majority of retrospective comparisons between surgery and SABR. This point also highlights the significance of the work by Chang and colleagues, as the first prospective comparison of SABR and lobectomy in equivalent populations.

Only recently have studies of SABR specific to medically-operable esNSCLC patients been reported. Recent studies, summarized in *Table 1*, include the current pooled analysis of multicenter phase III data by Chang *et al.* (1), the abstract publication of a North American multicenter phase II prospective trial (RTOG 0618) (6), a multicenter Japanese retrospective (8), and a single institution retrospective from the Netherlands (7). In aggregate the reports of SABR for operable esNSCLC demonstrate encouraging 3-year outcomes for OS (80-95%) and progression-free survival (PFS) (60-86%), in addition to estimated 3-year rates of local, regional, and distant failures rates in the range of 4-20%, 10-12%, and 3-20%, respectively. These outcomes compare well with contemporary outcomes for esNSCLC patients managed with surgery alone, where the 3-year OS rates for pT1-2 (<5 cm) N0 tumors are estimated at 70-90% (9). Grade 3 toxicities following SABR for operable esNSCLC have been observed in approximately 5-16% of patients, with no treatment-related deaths. Additional efforts to compare SABR and surgery in equivalent populations have been made using propensity score-matched analyses. In cohorts matched for factors such as age, tumor stage, pulmonary function, comorbidities, and performance status,

Table 2 Reported outcomes by Chang *et al.* (1) with SABR *vs.* lobectomy for medically-operable patients with esNSCLC

Outcomes	SABR	Lobectomy	P
Patients	31	27	
Median follow up	40.2 months	35.4 months	
Deaths	1	6	
1-year OS	100%	88%	
3-year OS	95%	79%	0.037
3-year RFS	86%	80%	0.54
Total recurrences	6	3	
Local	1	0	
Regional	4	1	
Distant	1	2	
3-year freedom from			
Local failure	96%	100%	0.44
Regional failure	90%	96%	0.32
Distant failure	97%	91%	0.42
Number of patients with toxicity [%]			
Grade 3	3 [10]	11 [41]	
Grade 4	0 [0]	1 [4]	
Grade 5	0 [0]	1 [4]	

SABR, stereotactic ablative radiotherapy; esNSCLC, early stage non-small cell lung cancer; OS, overall survival; RFS, recurrence-free survival.

survival outcomes between SABR and surgery have also appeared equivalent (10-12), with some data suggesting improved oncologic outcomes with SABR (13).

If one accepts the emerging data from Chang and others suggesting that similar survival outcomes may be achieved with SABR *vs.* lobectomy for esNSCLC; the next rational question is why? Paradoxically, the analysis by Chang *et al.* (*Table 2*) reports a nominally higher, though non-significant, difference in the number of recurrences following SABR (6 events) *vs.* surgery (3 events), whereas the survival outcomes favored SABR (1 death) over surgery (6 deaths). Inspection of Kaplan-Meier survival curves demonstrates an early separation related to deaths in the surgery group, followed by essentially parallel survival after 18 months.

The phenomenon of early survival curve separation in favor of radiation over surgery has been observed in a number of studies of NSCLC and is most often attributed to differences in treatment-related mortality. In the aforementioned propensity score-matched analyses, population-based data from the Amsterdam Cancer Registry (11) and SEER-Medicare claims data (12) comparing SABR and surgical resection each demonstrate an early OS advantage of SABR and a delayed advantage of surgery, leading to non-significant survival differences overall. Randomized trials in Stage IIIA-N2 NSCLC may also provide useful insights into this trend. An Intergroup trial in the US and Canada included patients receiving induction chemotherapy and 45 Gy of conventionally-fractionated radiation (CFRT) who were randomized to completion of definitive radiation to a total dose of 61 Gy *vs.* definitive surgical resection (14). An EORTC study randomized patients with response to induction chemotherapy to definitive CFRT or surgery (15). Both of these trials demonstrated an early separation of the survival curves in favor of radiation over surgery, followed by a crossing of the curves between 12 and 36 months, with long-term outcomes non-significantly in favor of surgery. Surgery was associated with an approximate 50% relative reduction in locoregional failures in both trials and statistically significant improvement in PFS in the Intergroup trial.

In each of the studies above, the early separation of the survival curves was attributed to perioperative mortality, while the delayed advantages of surgery were attributed to superior oncologic control; with an overall effect being non-significant differences in OS between groups. Recognizing the apparent oncologic advantage of surgery over definitive CFRT, the authors of the Intergroup trial performed an unplanned subgroup analysis showing a benefit of surgery in patients undergoing lobectomy rather than pneumonectomy, as the latter was associated with greater perioperative mortality (14). The critical difference between these randomized trials and the data presented by Chang (1) is that SABR for esNSCLC is a far better local therapy, associated with local control rates of ≥80-90% in large series (16), compared to CFRT to the lung and mediastinum for Stage IIIA NSCLC, where 50-60% of patients will develop locoregional failures (14,15,17). In light of the early survival advantage afforded to SABR by perioperative mortality, significant survival advantages are likely to be observed in studies where SABR can perform at equivalent, or even near-equivalent, oncologic levels to lobectomy for esNSCLC. We refer to this phenomenon as the "Head Start Effect".

Operative mortality estimates vary among studies, but are generally reported in the range of 1-4% at 30 days and 2-6% at 90 days following lobectomies for NSCLC (18,19). Baseline mortality risks may be approximately doubled in

the setting of pneumonectomy or advanced age, and may be significantly decreased when performed at high-volume centers and in the hands of experienced surgeons (20). Estimates of treatment-related mortality following SABR for esNSCLC have been reported at 0.6% and are frequently absent from contemporary studies following the adoption of conservative dose schedules for centrally located tumors (21,22). In the analysis by Chang (1), it is important to note that only 5 of 27 patients in the surgical cohort underwent a video-assisted thoracoscopic (VATs) lobectomy, and a recent meta-analysis suggests that improved 5-year OS maybe achievable with VATs over open lobectomy (23). Although, at least in this study, even if no patients died due to operative mortality (one) or comorbidities (two) following lobectomy, these differences would have only made the survival outcomes more similar to SABR, but no better.

For future trials of esNSCLC, potential differences in treatment-related mortality beyond conventional time frames of 30 or 90 days may also begin to play a more prominent role in differentiating outcomes between modalities. A report from the National Cancer Database involving 124,418 major pulmonary resections at 1,233 facilities reported ongoing perioperative mortality hazard between 30 and 90 days as an important risk for NSCLC patients undergoing resection (19). However, there is a general paucity of data correlating mortality to operative risk beyond the 90-day mark (24), which may be attributable to the near-absence of randomized data comparing surgical and non-surgical approaches in equivalent esNSCLC populations. Reported rates of surgical complications following lung resections are generally in the range of 30-40% (25). Major surgical complications include arrhythmias, myocardial infarction, respiratory failure, infections, pneumothorax, DVT, and PE, which may be observed in addition to expected decreases in pulmonary function and the promotion of a global pro-inflammatory state (25,26). While most of these complications will not directly lead to mortality during a conventional perioperative period, it is conceivable that they may contribute to a meaningful increase in subacute and delayed mortality hazard in esNSCLC populations with fundamentally limited cardiopulmonary reserve, often presenting with advanced age, heavy smoking histories, and comorbid heart and lung disease.

Until adequately powered randomized trials are completed, reasonable objections to purported equivalence, or potential advantages, of SABR in comparison to lobectomy for esNSCLC will surely remain. Conceptually, it is difficult to accept that SABR, which intends to treat only the tumor with a margin of normal surrounding tissue, could be oncologically equivalent to the removal of a the tumor and tumor-involved lobe of the lung. After all, a landmark randomized trial of lobectomy *vs.* sublobar resection demonstrated a 3-fold increase in local failures and a strong trend toward inferior OS and cancer-specific survival with sub-lobar therapy (27). If we assume that potential off-target immune enhancement (so-called 'abscopal effects') following SABR and potential scattered radiation dose to microscopic disease in hilar or mediastinal lymph nodes do not translate into clinically meaningful benefits, we would submit that SABR and lobectomy are likely not to be equivalent oncologic therapies—at least in terms of local tumor control. Focusing first on the involved lobe, a lobectomy should, in theory, provide 100% in-lobe tumor control. In a hypothetical scenario where SABR provided 100% treated-tumor control, the in-lobe control away from the SABR target will always be less than 100% in an adequately powered study. In illustration of this point, the RTOG 0236 trial of SABR of inoperable esNSCLC reported outstanding 3-year local control rates of 98% at the treated tumor, while in-lobe non-target failures occurred in an additional 7% of patients at 3 years (28) and 13% at the 5-year mark (29). With regards to regional control, hilar and mediastinal nodal dissections (or sampling) in conjunction with lobectomy may potentially reduce regional nodal recurrences in patients undergoing surgery *vs.* SABR; although, interestingly the 5-year regional failure rates with SABR observed in the range of 7-15% are quite comparable to surgical series (7,29,30). Overall, the window of opportunity for lobectomy to outperform SABR in terms of cancer-specific survival would presumably be found in these potential differences in isolated locoregional failures (that is, without concurrent distant failures) between the two local treatment modalities. However, in the largest available series of SABR for esNSCLC involving 676 patients, isolated locoregional failures were observed in only 6% (42 patients) (13), suggesting a relatively narrow window for surgery to establish superiority in terms of cancer-specific survival. Moreover, it is also reasonable to assume that as more medically-operable patients with esNSCLC are treated with SABR, a greater number of isolated locoregional SABR failures will be surgically-salvageable (31,32). This concept is somewhat analogous to the successful application of salvage mastectomies for

recurrent breast cancer after upfront lumpectomy and radiation (33).

There are several additional criticisms of merit regarding the use of SABR for operable esNSCLC, including the frequent use of SABR for patients without a histologic diagnosis and the clinical implications of pathologic upstaging of patients undergoing resection of esNSCLC. In the Chang paper (1), the STARS protocol required histologic confirmation for enrollment, whereas the ROSEL protocol did not, given that the reported likelihood of pathologically benign disease in the setting of radiographic features consistent with malignant disease was estimated to be less than 6% in the Dutch population (34). Notably, the largest analysis on the subject, including 591 patients treated with SABR for histologically-confirmed (209 patients) and clinical-only (382 patients) esNSCLC, demonstrated no differences in survival or local, regional, or distant control between groups (35). Given that a portion of patients will also undergo surgery without preoperative histologic-confirmation when malignancy is strongly suspected (36), non-invasive SABR may carry certain advantages for patients with benign disease in terms of treatment-related morbidity and mortality. On the other hand, surgical resection would ultimately be expected to spare such patients from years of oncologic follow up and anxiety once benign disease is identified (37). For patients with NSCLC, it must also be acknowledged that a wealth of molecular, histologic, and other prognostic information can only be obtained pathologically via either resection or biopsy (36). Finally, despite similar regional recurrence rates following SABR and lobectomy with nodal evaluation (8), nodal upstaging may be observed in as many as 19% of patients following definitive resection and may provide critical information for the guidance of adjuvant therapy (38). Together, these issues underscore the value of pursuing a histologic diagnosis prior to planned SABR delivery, as well as the utility of pre-treatment mediastinal staging procedures in suitable candidates (39), similar to approaches used prior to definitive surgery.

Although small in numbers, the data reported by Chang and colleagues have substantial disruptive implications regarding our time honored approach of surgery-until-proven-otherwise for esNSCLC. In a gathering state of equipoise, as suggested by Chang and others (1,7,8), adequately powered clinical trials comparing lobectomy and SABR for this population are now clearly needed. For thoracic oncologists treating NSCLC, the most common malignancy in men and women combined, it is useful to consider the example set by the landmark trials of breast conservation (40), or we may risk the fate of localized-prostate cancer management—with commendable surgical and radiotherapy options—but no understanding of how they might fare, or what cohorts might benefit most from a given modality, when compared in a well-designed, adequately powered randomized trial (41).

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. 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.
2. Onishi H, Araki T. Stereotactic body radiation therapy for stage I non-small-cell lung cancer: a historical overview of clinical studies. Jpn J Clin Oncol 2013;43:345-50.
3. Soldà F, Lodge M, Ashley S, et al. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic review and comparison with a surgical cohort. Radiother Oncol 2013;109:1-7.
4. British Thoracic Society; Society of Cardiothoracic Surgeons of Great Britain and Ireland Working Party. BTS guidelines: guidelines on the selection of patients with lung cancer for surgery. Thorax 2001;56:89-108.
5. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100.
6. Timmerman RD, Paulus R, Pass HI, et al. RTOG 0618: Stereotactic body radiation therapy (SBRT) to treat operable early-stage lung cancer patients. J Clin Oncol 2013;31:abstr 7523.
7. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:348-53.
8. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352-8.
9. Rami-Porta R, Ball D, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the

T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol 2007;2:593-602.
10. Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2010;140:377-86.
11. Palma D, Visser O, Lagerwaard FJ, et al. Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery. Radiother Oncol 2011;101:240-4.
12. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. JAMA Surg 2014;149:1244-53.
13. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 2013;24:1543-8.
14. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379-86.
15. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007;99:442-50.
16. Senthi S, Lagerwaard FJ, Haasbeek CJ, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol 2012;13:802-9.
17. Curran WJ, Paulus R, Langer CJ, et al. Sequential vs concurrent chemoradiation for stage III non–small cell lung cancer: randomized Phase III trial RTOG 9410. J Natl Cancer Inst 2011;103:1452-60.
18. Bryant AS, Rudemiller K, Cerfolio RJ. The 30-versus 90-day operative mortality after pulmonary resection. Ann Thorac Surg 2010;89:1717-22; discussion 1722-3.
19. Pezzi CM, Mallin K, Mendez AS, et al. Ninety-day mortality after resection for lung cancer is nearly double 30-day mortality. J Thorac Cardiovasc Surg 2014;148:2269-77.
20. Hannan EL, Radzyner M, Rubin D, et al. The influence of hospital and surgeon volume on in-hospital mortality for colectomy, gastrectomy, and lung lobectomy in patients with cancer. Surgery 2002;131:6-15.
21. Grutters JP, Kessels AG, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. Radiother Oncol 2010;95:32-40.
22. Nagata Y, Hiraoka M, Mizowaki T, et al. Survey of stereotactic body radiation therapy in Japan by the Japan 3-D Conformal External Beam Radiotherapy Group. Int J Radiat Oncol Biol Phys 2009;75:343-7.
23. Chen FF, Zhang D, Wang YL, et al. Video-assisted thoracoscopic surgery lobectomy versus open lobectomy in patients with clinical stage non-small cell lung cancer: a meta-analysis. Eur J Surg Oncol 2013;39:957-63.
24. Discussion. J Thorac Cardiovasc Surg 2014;148:2277-8.
25. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. Ann Thorac Surg 2006;81:1013-9; discussion 1019-20.
26. Nagahiro I, Andou A, Aoe M, et al. Pulmonary function, postoperative pain, and serum cytokine level after lobectomy: a comparison of VATS and conventional procedure. Ann Thorac Surg 2001;72:362-5.
27. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
28. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
29. Timmerman RD, Hu C, Michalski J, et al. Long-term Results of RTOG 0236: A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2014;90:S30.
30. Lou F, Huang J, Sima CS, et al. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg 2013;145:75-81; discussion 81-2.
31. Bradley J. New territory: surgical salvage for stereotactic body radiation therapy failures in lung cancer. J Thorac Oncol 2010;5:1879-80.
32. Chen F, Matsuo Y, Yoshizawa A, et al. Salvage lung resection for non-small cell lung cancer after stereotactic body radiotherapy in initially operable patients. J Thorac Oncol 2010;5:1999-2002.
33. Abner AL, Recht A, Eberlein T, et al. Prognosis following

salvage mastectomy for recurrence in the breast after conservative surgery and radiation therapy for early-stage breast cancer. J Clin Oncol 1993;11:44-8.
34. Verstegen NE, Lagerwaard FJ, Senan S. Developments in early-stage NSCLC: advances in radiotherapy. Ann Oncol 2012;23:x46-51.
35. Verstegen NE, Lagerwaard FJ, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy following a clinical diagnosis of stage I NSCLC: comparison with a contemporaneous cohort with pathologically proven disease. Radiother Oncol 2011;101:250-4.
36. Ettinger DS, Wood DE, Akerley W, et al. Non-Small Cell Lung Cancer, Version 6.2015. J Natl Compr Canc Netw 2015;13:515-24.
37. Montazeri A, Milroy R, Hole D, et al. Anxiety and depression in patients with lung cancer before and after diagnosis: findings from a population in Glasgow, Scotland. J Epidemiol Community Health 1998;52:203-4.
38. Licht PB, Jørgensen OD, Ladegaard L, et al. A national study of nodal upstaging after thoracoscopic versus open lobectomy for clinical stage I lung cancer. Ann Thorac Surg 2013;96:943-9; discussion 949-50.
39. Sarwate D, Sarkar S, Krimsky WS, et al. Optimization of mediastinal staging in potential candidates for stereotactic radiosurgery of the chest. J Thorac Cardiovasc Surg 2012;144:81-6.
40. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233-41.
41. Welz S, Nyazi M, Belka C, et al. Surgery vs. radiotherapy in localized prostate cancer. Which is best? Radiat Oncol 2008;3:23.

Cite this article as: Rusthoven CG, Kavanagh BD, Karam SD. Improved survival with stereotactic ablative radiotherapy (SABR) over lobectomy for early stage non-small cell lung cancer (NSCLC): addressing the fallout of disruptive randomized data. Ann Transl Med 2015;3(11):149. doi: 10.3978/j.issn.2305-5839.2015.06.15

Controversy and Debate

Stereotactic ablative radiotherapy (SABR) in operable early stage non-small cell lung cancer (NSCLC) patients: challenge to claim being undisputed gold standard

Deniz Yalman[1], Ugur Selek[2,3]

[1]Department of Radiation Oncology, Ege University, School of Medicine, Izmir, Turkey; [2]Department of Radiation Oncology, Koç University, School of Medicine, Istanbul, Turkey; [3]Department of Radiation Oncology, University of Texas, MD Anderson Cancer Center, Houston, TX, USA
Correspondence to: Deniz Yalman. Department of Radiation Oncology, Ege University, School of Medicine, 35100 Bornova-Izmir, Turkey. Email: yalman.deniz@gmail.com.

Submitted Jun 23, 2015. Accepted for publication Jun 25, 2015.
doi: 10.3978/j.issn.2305-5839.2015.06.23
View this article at: http://dx.doi.org/10.3978/j.issn. 2305-5839.2015.06.23

The standard treatment for operable, early stage non-small cell lung cancer (NSCLC) is surgical resection, usually lobectomy, with mediastinal lymph node sampling or dissection. However, significant surgical toxicity had been noted in these patients with 90-day mortality rates exceeding 30-day rates (1). There is also a risk of disease recurrence ranging from 6% to 10% per person-year during the first 4 years after surgery as stated by Lou *et al*. after an analysis of 1,300 patients who underwent surgery (2).

A substantial proportion of early-stage lung cancer patients are not suitable for surgery due to their coexisting serious medical problems, older age, and poor performance status. Conventional radiotherapy is only modestly effective in these patients. Over the past decade, stereotactic body radiation therapy (SBRT), which uses highly conformal multiple noncoplanar beams for the precise delivery of high doses per fraction, has emerged as a promising treatment alternative in the management of these frail patients with early-stage disease with acceptable outcomes noted to be better than conventional radiotherapy. In recent years, the prescription of truly ablative radiation doses has been professed as stereotactic ablative radiotherapy (SABR) (3,4). Several technological advances in patient positioning and immobilization systems, tumor motion assessment and control, target delineation, image guidance for precise targeting, and treatment planning systems facilitated the use of SABR in the treatment of many organ cancers and metastases. The delivery of very high biologically effective doses in a fewer actual treatments is also more convenient for the patients.

There has been an ongoing evolution in SABR to define the toxicity and efficiency limits to be safely delivered. As many medically inoperable patients have limited lung functions, it was relieving to observe that SABR for medically inoperable stage I lung cancer did not cause any major deterioration in pulmonary function tests even in severe chronic obstructive pulmonary disease (5,6). Another step was to define the minimum dose of SABR for local control, and Onishi and colleagues draw the line for better local control and survival rates with a minimum calculated biological effective dose (BED) of 100 Gy in their Japanese multi-institutional study (7). On defining the safety limits, Timmerman *et al*. reported excessive toxicity when treating centrally located tumors near the central airways with 54-60 Gy in 3 fractions, and determined a "SABR no-fly zone" (8). However, risk-adapted SABR schedules were reported to be considered safe in this zone with well tolerability and less toxicity via more than 3 fractions of SABR and more detailed recommendations have been announced to delineate how to fly in a "no fly zone" by SABR (9,10). As the ongoing Radiation Therapy and Oncology Group (RTOG) 0813 phase I trial for centrally located tumors is expected to determine the maximum tolerated dose in 5 fractions based on risk-adapted dosing strategies Advanced Radiation Technology Committee of the International Association for the Study of Lung Cancer recently published the up-to-date boundaries of indications, dose regimens, planning optimization, and normal tissue dose-volume constraints for 4, 5, and 10 fractions including critical structures such

as bronchial tree, esophagus, major vessels, heart, and the brachial plexus/phrenic nerve for prescribing SABR to treat central NSCLC (11).

The landmark study RTOG 0236 determined the role of SABR for medically inoperable patients with moderate treatment-related morbidity. RTOG 0236 trial with 34.4 months of follow-up indicated a 3-year primary tumor control rate of 98%, a locoregional control rate of 87%, 3-year local (tumor plus lobe) control rate of 91%, and a median overall survival (OS) of 48 months in 55 medically inoperable, peripherally located early-stage NSCLC patients (12). The survival contribution of SABR to these surgically untouchable patients whose natural survival history without treatment would be a median of 13 months for a T1N0M0 patient was encouraging (13). Multiple similar retrospective or prospective studies from several cooperative groups around the world reported similar local control and survival rates with several total dose and fractionation schemes (9,14-16). The results of these studies have clearly proven that SABR should be the new standard treatment for patients with early-stage NSCLC who are unable to tolerate surgery.

Despite encouraging results in medically inoperable patients the introduction of SABR to operable early stage patients instead of gold standard surgery has been a challenging issue. On one hand there is an invasive but a proven treatment option, and on the other hand there is a noninvasive, more convenient but an unproven treatment option leading to similar results. The search for whether similar promising outcomes could be observed in medically operable patients started with retrospective analysis of series including potentially operable patients. Onishi *et al.* retrospectively pointed out successful results for medically operable early stage NSCLC patients in their multi-institutional database, while Lagerwaard *et al.* emphasized a more than 5 years median OS for patients with potentially operable disease who underwent primary SABR (17,18). The Japan Clinical Oncology Group (JCOG) documented their phase II trial of SABR (JCOG 0403) for operable peripheral stage IA NSCLC with a 3-year survival rate of 76% and a 3-year locally progression-free survival rate of 69% in patients with a median age of 79 years old (19).

As there was no prospective randomized data on SABR, series and retrospective reviews using matched-pair analysis and propensity score comparisons, and a systematic review in clinical stage I NSCLC treated with surgery or SABR were published after 2012 (20-22). Interestingly these series reported no differences in OS, local or locoregional control between surgery and SABR, and even superior locoregional control with SABR. A recent survival meta-analysis covering 40 SABR studies (4,850 patients) and 23 surgery studies (7,071 patients) also pointed out no difference in OS and disease free survival after adjustment for age and operability in operable stage I NSCLC (23).

These provocative results have led to the initiation of three randomised trials comparing SABR with lobectomy (STARS, ROSEL) or sublobar resection (ACOSOG Z4099/RTOG 1021) in order to finalize the challenge between surgery and SABR in operable patients. Radiation oncologists and thoracic surgeons have been waiting the results of these randomised trials eagerly in order to call time on the argument about the issue of SABR or surgery for operable stage I patients. However, both due to the limited number of operable patients and the reluctance of patients and doctors for randomisation between two completely different treatments, these trials were terminated early due to poor accrual, and no report was published about these trials until the current paper by Chang *et al.* which reported the combined results of randomized STARS and ROSEL trials comparing SABR with lobectomy for operable stage I patients (24). The authors are to be congratulated for their effort combining the data of these two trials. Fifty-eight patients with clinical T1-T2a (<4 cm), N0M0, operable NSCLC were enrolled and randomly assigned to SABR (31 patients) or lobectomy with mediastinal lymph node dissection or sampling (27 patients). Histological confirmation of NSCLC was required in the STARS trial but was not mandatory in the ROSEL trial which included only Dutch patients. In the STARS protocol CyberKnife system was used to deliver SABR, whereas linac-based SABR from multiple vendors was used in the ROSEL protocol. In the STARS trial 54 Gy in 3 fractions in peripherally located tumors, and 50 Gy in 4 fractions in central lesions were applied. In the ROSEL trial 54 Gy in 3 fractions or 60 Gy in 5 fractions were applied. Median follow-up for all patients was 40.2 months in the SABR group and 35.4 months in the surgery group. Pooled estimated OS at 3 years favored SABR group (95% *vs.* 79%; P=0.037). The difference in OS between two groups was significant in STARS alone (P=0.0067) but not in ROSEL (P=0.78). One patient in the SABR group, and two patients in the surgery group had distant metastasis at 3 years (P=0.42). Recurrence-free survival at 3 years also favored SABR group but the difference was not significant (86% *vs.* 80%; P=0.54). At 3 years 96% of patients were free from local recurrence in the SABR group compared

with 100% of patients in the surgery group (P=0.44). But the statistical power of this study to detect significant differences in terms of local, regional, and distant failure between the two groups was low due the small number of events in a small patient population with a short follow-up duration. Only one death occurred within the SABR group in contrast to six deaths in the surgery group; and the lower survival rate following surgery was suggested to be related with other co-existing conditions worsened by the surgical reduction of lung function. Three patients (10%) in the SABR group developed grade 3 treatment-related toxicity without any grade 4 or 5 toxicity seen. One patient (4%) in the surgical group died of surgical complications and 12 patients (44%) had grade 3-4 treatment-related toxicity.

One of the common criticisms for SABR studies has been lack of tissue diagnosis before treatment. In this current pooled analysis, this issue could be brought up as histological confirmation by biopsy or cytological evaluation was necessary in the STARS trial whereas was not mandatory in the ROSEL protocol. But numerous studies already clearly justified the treatment without a pathologic diagnosis if a tissue diagnosis is not possible to safely obtain and there is enough clinical, and/or metabolic/radiographic evidence to predict progressive tumor (25,26). On the other hand, the tissue diagnosis could be pursued in an operable patient population in future trials which would still be a great contribution for future possible personalized medical treatment based on molecular/genetic prognostic and predictive biomarkers for targeted medications. Then again, the lack of surgical staging (mediastinal sampling, dissection) in SABR patients, aside from clinical staging with CT, PET-CT, and endobronchial ultrasonography, did not cause any deterioration in locoregional control or OS with SABR in this pooled analysis, and a surgical myth on criticizing radiation oncologists is almost over.

The findings of this study are consistent with the findings from the previous studies concluding that two treatment options are at least equal and SABR should also be considered as a treatment option in operable stage I patients. Finally the results of this study are encouraging the clinicians to facilitate a large clinical trial to investigate a fair comparison of SABR versus surgery in early-stage operable NSCLC patients after lost years of discussion to limit SABR in only medically inoperable patients.

One can claim that it is time to have another big step in the treatment evolution of early stage NSCLC which might add SABR as equipoise gold standard to the standing alone gold standard surgery. According to the reported data so far, good oncologic outcome, and low toxicity of SABR will lead to limitation of the use of surgery in the treatment of stage I NSCLC in the future.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Bryant AS, Rudemiller K, Cerfolio RJ. The 30- versus 90-day operative mortality after pulmonary resection. Ann Thorac Surg 2010;89:1717-22.
2. Lou F, Huang J, Sima CS, et al. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg 2013;145:75-81.
3. Loo BW Jr. Stereotactic ablative radiotherapy (SABR) for lung cancer: What does the future hold? J Thorac Dis 2011;3:150-2.
4. Loo BW Jr, Chang JY, Dawson LA, et al. Stereotactic ablative radiotherapy: what's in a name? Pract Radiat Oncol 2011;1:38-9.
5. Palma D, Lagerwaard F, Rodrigues G, et al. Curative treatment of stage I non-small-cell lung cancer in patients with severe COPD: stereotactic radiotherapy outcomes and systematic review. Int J Radiat Oncol Biol Phys 2012;82:1149-56.
6. Stephans KL, Djemil T, Reddy CA, et al. Comprehensive analysis of pulmonary function test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. J Thorac Oncol 2009;4:838-44.
7. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100.
8. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
9. Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;70:685-92.
10. Chang JY, Li QQ, Xu QY, et al. Stereotactic ablative

radiation therapy for centrally located early stage or isolated parenchymal recurrences of non-small cell lung cancer: how to fly in a "no fly zone". Int J Radiat Oncol Biol Phys 2014;88:1120-8.
11. Chang JY, Bezjak A, Mornex F. Stereotactic ablative radiotherapy for centrally located early stage non-small-cell lung cancer: what we have learned. J Thorac Oncol 2015;10:577-85.
12. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
13. Raz DJ, Zell JA, Ou SH, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. Chest 2007;132:193-9.
14. Shibamoto Y, Hashizume C, Baba F, et al. Stereotactic body radiotherapy using a radiobiology-based regimen for stage I nonsmall cell lung cancer: a multicenter study. Cancer 2012;118:2078-84.
15. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75:677-82.
16. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small cell lung cancer patients treated w$th stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.
17. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352-8.
18. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:348-53.
19. Onishi H, Araki T. Stereotactic body radiation therapy for stage I non-small-cell lung cancer: a historical overview of clinical studies. Jpn J Clin Oncol 2013;43:345-50.
20. Varlotto J, Fakiris A, Flickenger J, et al. Matched-pair and propensity score comparisons of outcomes of patients with clinical stage I non-small cell lung cancer treated with resection or stereotactic radiosurgery. Cancer 2013;119:2683-91.
21. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 2013;24:1543-8.
22. Soldà F, Lodge M, Ashley S, et al. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic review and comparison with a surgical cohort. Radiother Oncol 2013;109:1-7.
23. Zheng X, Schipper M, Kidwell K, et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis. Int J Radiat Oncol Biol Phys 2014;90:603-11.
24. 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.
25. Verstegen NE, Lagerwaard FJ, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy following a clinical diagnosis of stage I NSCLC: comparison with a contemporaneous cohort with pathologically proven disease. Radiother Oncol 2011;101:250-4.
26. Inoue T, Shimizu S, Onimaru R, et al. Clinical outcomes of stereotactic body radiotherapy for small lung lesions clinically diagnosed as primary lung cancer on radiologic examination. Int J Radiat Oncol Biol Phys 2009;75:683-7.

Cite this article as: Yalman D, Selek U. Stereotactic ablative radiotherapy (SABR) in operable early stage non-small cell lung cancer (NSCLC) patients: challenge to claim being undisputed gold standard. Ann Transl Med 2015;3(11):150. doi: 10.3978/j.issn.2305-5839.2015.06.23

Controversy and Debate

Stereotactic ablative radiotherapy and surgery: two gold standards for early-stage non-small cell lung cancer?

Hanbo Chen, Alexander V. Louie

Department of Radiation Oncology, London Regional Cancer Program, Western University, London, ON, Canada
Correspondence to: Dr. Alexander V. Louie, MD, MSc, FRCPC. Department of Radiation Oncology, 790 Commissioners Road East, London Regional Cancer Program, N6A 4L6, London, ON, Canada. Email: dr.alexlouie@gmail.com.

Abstract: There is growing clinical equipoise between surgery and stereotactic ablative radiotherapy (SABR) in the management of early-stage non-small cell lung cancer (ES-NSCLC). Increasing evidence suggest similar outcomes between these modalities. Through the guidance of a multidisciplinary team, a shared decision making approach in this setting in favoured.

Keywords: Carcinoma; non-small cell lung; comparative effectiveness research; radiosurgery; retrospective studies; thoracic surgical procedures

Submitted May 21, 2015. Accepted for publication May 22, 2015.
doi: 10.3978/j.issn.2305-5839.2015.05.08
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.05.08

Early-stage (T1-T2aN0M0) non-small cell lung cancer (ES-NSCLC) has been successfully treated with surgery for decades, with an anatomic lobectomy established as the treatment of choice for localized disease in operable patients since the 1960s (1). Though sublobar resections via wedge resections or segmentectomies were originally found to be less effective than lobectomies in terms of local control (LC) and overall survival (OS) in the 1990s (2), this concept has been challenged by more recent studies, mostly comprised of elderly patients with compromised pulmonary function (3-5). As such, sublobar resections are currently endorsed by multiple clinical practice guidelines (6,7) as a first-line treatment option for borderline operable patients with poor pulmonary function or multiple comorbidities.

For ES-NSCLC patients who are medically inoperable, non-surgical alternatives such as conventionally fractionated radiotherapy have traditionally been regarded as superior to no treatment, but were not able to achieve similar levels of LC or OS as surgical resection. With the advent of stereotactic ablative radiotherapy (SABR, also known as stereotactic body radiation therapy—SBRT) around the turn of the century, however, radiation oncologists have been able to deliver higher, tumor-ablative doses of radiation (biological effective dose >100 Gy) in fewer fractions with a high degree of accuracy. This has been made possible through advancements in motion management, image guidance and radiation delivery systems. Early evidence with population-level retrospective time-trend studies on the effectiveness of SABR has demonstrated a correlation of improved OS with the introduction of SABR (8,9). Prospective single-arm clinical trial data on the efficacy of SABR on medically inoperable (10) and operable ES-NSCLC patients (11) have also demonstrated LC and OS rates comparable to historical surgical outcomes (2).

Considering such evidence in the PET-staging era, there has been a sense of growing equipoise that argues for SABR as an alternate to surgery for operable ES-NSCLC (12). Randomized control trial (RCT) evidence based on today's technology and techniques comparing SABR and surgery in operable patients ES-NSCLC would afford the highest level of evidence. Three RCTs have been proposed (ROSEL, STARS, RTOG 1021/ACOSOG Z4099) within the past decade comparing SABR to standard surgical management options for ES-NSCLC, though all have closed prematurely due to poor accrual. This is often the case when treatments offered in a RCT differ significantly from the current paradigm, and both options are otherwise available off study (13,14).

In situations where RCTs are unavailable, other forms of well-controlled, comparative effectiveness research take on the mantle of informing patient and physician decision-

making. Indeed, a number of studies consisting of single-institution retrospective data, which contain inherent biases, have been published regarding the use of SABR in operable ES-NSCLC patients, with mixed results (15,16). Seeking to reduce these biases, the recent study by Shirvani *et al*. (17) is an example of a high-quality, retrospective, SEER-Medicare population-based study that compared the outcomes for surgery and SABR with propensity score-matched analysis. The usage of population-level data overcomes biases from different practice patterns based on geographical location and makes the study results more generalizable. Propensity-score analysis also compensates for confounding by indication via the assignment of propensity scores to individual patients based on their baseline characteristics. Only patients with similar propensity scores from each group are then subsequently compared. Of note, surgical management in this study was stratified into lobectomy and sublobar resection, and lobectomy was used as the standard against which both SABR and sublobar resection were compared. Sublobar resection was not further stratified into segmentectomy and wedge resections due to limitations of the SEER database. This interestingly precluded direct comparison between sublobar resection and SABR, between which currently there is arguably the greatest sense of clinical equipoise (18).

With this approach, Shirvani *et al*. were able to provide valuable insight into the ongoing debate of surgery *vs*. SABR. First of all, the population-level data reiterates the significant differences in baseline characteristics between lobectomy, sublobar resection and SABR patients. For example, compared to lobectomy patients, SABR patients were more likely to be octogenarian, female, have a higher Charlson Comorbidity Index, require supplemental oxygen and have poorer performance. Also, SABR patients were more likely to be PET-staged and much less likely to have received procedure-based mediastinal staging. In unadjusted analyses, lobectomy was shown to have improved OS when compared to sublobar resection or SABR in the long term (>6 months), perhaps related to the older age and higher level of comorbidity in sublobar resection and SABR patients. In a subset analysis, SABR was found to have significantly higher patient OS within 6 months of treatment compared to lobectomy, which highlights the importance of considering treatment related mortality in this context (19).

With propensity-score matched analysis, however, there were no significant differences in OS and disease-specific survival (DSS) between lobectomy and SABR in balanced populations, though there was a non-statistically significant trend towards improved OS and DSS for lobectomy greater than 12 months after treatment. In terms of lobectomy *vs*. sublobar resection, there was a clear benefit for lobectomy for both OS and DSS with propensity-score matched analysis.

There were some limitations in the Shirvani *et al*. study. The SEER-Medicare database only includes patients using the fee-for-service Medicare services and may not comprehensively include some patients of African-American ethnicity, female gender and/or lower socioeconomic status, as these patients are more likely to seek enrollment in Health Maintenance Organizations (HMOs) (20,21). The database also only includes patients greater than 65 years of age. Data on local and regional control/recurrence and treatment-related toxicity would also have been useful in informing other risk/benefit trade-offs between surgery and SABR. These limitations, however, do not diminish this study's ability to contribute to the growing equipoise of the use of SABR in ES-NSCLC due to its overall large sample size and appropriate statistical analyses. Interestingly, another study with a similar study design using the SEER-Medicare database was published soon after the present study (22). This latter study comprised of a more restricted time period from 2007 to 2009, and performed propensity matching of similar patient factors, but not on tumor factors such as T-stage or histology. The DSS of surgery (lobectomy and sublobar resection were again not differentiated) did not differ from SABR at 24 months, though there was an OS advantage using surgery following 24 months. There was an OS advantage for SABR up to 3 months after treatment, again highlighting treatment-related mortality differences between the two modalities.

There is an increasing body of retrospective evidence that suggests equipoise between SABR and surgery for operable patients with ES-NSCLC. Most recently, ongoing analyses with pooled results from the prematurely-closed RCTs have also shown promising results of comparable outcomes between SABR and surgery in terms of recurrence-free survival, locoregional control and distant control (23). Furthermore, despite the small sample size of this pooled analysis, there was an OS benefit in patients treated with SABR. It is foreseeable that in the near future these studies will lead to increased multidisciplinary discussion of treatment options for ES-NSCLC patients. When there is equipoise on clinical management, shared decision-making is becoming increasingly popular, where the patient is given guidance by experts who are familiar with the pros and cons of each option and attempt to explore the patient's

underlying preferences for cancer treatment in light of the available evidence (24).

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Shimkin MB, Connelly RR, Marcus SC, et al. Pneumonectomy and lobectomy in bronchogenic carcinoma. A comparison of end results of the Overholt and Ochsner clinics. J Thorac Cardiovasc Surg 1962;44:503-19.
2. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
3. Mery CM, Pappas AN, Bueno R, et al. Similar long-term survival of elderly patients with non-small cell lung cancer treated with lobectomy or wedge resection within the surveillance, epidemiology, and end results database. Chest 2005;128:237-45.
4. Takizawa T, Haga M, Yagi N, et al. Pulmonary function after segmentectomy for small peripheral carcinoma of the lung. J Thorac Cardiovasc Surg 1999;118:536-41.
5. Harada H, Okada M, Sakamoto T, et al. Functional advantage after radical segmentectomy versus lobectomy for lung cancer. Ann Thorac Surg 2005;80:2041-5.
6. Ettinger DS, Wood DE, Akerley W, et al. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology – Non-small cell lung cancer. National Comprehensive Cancer Network, 2015. Available online: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf, accessed May 2 2015.
7. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e278S-313S.
8. Haasbeek CJ, Palma D, Visser O, et al. Early-stage lung cancer in elderly patients: a population-based study of changes in treatment patterns and survival in the Netherlands. Ann Oncol 2012;23:2743-7.
9. Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. J Clin Oncol 2010;28:5153-9.
10. Nagata Y, Hiraoka M, Shibata T, et al. A Phase II Trial of Stereotactic Body Radiation Therapy for Operable T1N0M0 Non-small Cell Lung Cancer: Japan Clinical Oncology Group (JCOG0403) [Abstract]. Int J Radiat Oncol Biol Phys 2010;78:s27-8.
11. Timmerman RD, Paulus R, Pass HI, et al. RTOG 0618: stereotactic body radiation therapy (SBRT) to treat operable early-stage lung cancer patients. J Clin Oncol 2013;31:7523.
12. Senan S, Paul MA, Lagerwaard FJ. Treatment of early-stage lung cancer detected by screening: surgery or stereotactic ablative radiotherapy? Lancet Oncol 2013;14:e270-4.
13. Wallace K, Fleshner N, Jewett M, et al. Impact of a multi-disciplinary patient education session on accrual to a difficult clinical trial: the Toronto experience with the surgical prostatectomy versus interstitial radiation intervention trial. J Clin Oncol 2006;24:4158-62.
14. Hamilton EP, Lyman GH, Peppercorn J. Availability of experimental therapy outside oncology randomized clinical trials in the United States. J Clin Oncol 2010;28:5067-73.
15. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352-8.
16. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:348-53.
17. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. JAMA Surg 2014;149:1244-53.
18. Shah A, Hahn SM, Stetson RL, et al. Cost-effectiveness of stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. Cancer 2013;119:3123-32.
19. Louie AV, Rodrigues G, Hannouf M, et al. Stereotactic body radiotherapy versus surgery for medically operable Stage I non-small-cell lung cancer: a Markov model-based decision analysis. Int J Radiat Oncol Biol Phys 2011;81:964-73.
20. Virnig BA, Morgan RO, DeVito CA, et al. Medicare HMOs: who joins and who leaves? Am J Manag Care 1998;4:511-8.
21. SEER-Medicare: Data Limitations. Division of Health Delivery Research, National Cancer Institute. Available

online: http://healthcaredelivery.cancer.gov/seermedicare/considerations/limitations.html, accessed May 2 2015.
22. Yu JB, Soulos PR, Cramer LD, et al. Comparative effectiveness of surgery and radiosurgery for stage I non-small cell lung cancer. Cancer 2015. [Epub ahead of print].
23. 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. [Epub ahead of print].
24. Elwyn G, Frosch D, Thomson R, et al. Shared decision making: a model for clinical practice. J Gen Intern Med 2012;27:1361-7.

Cite this article as: Chen H, Louie AV. Stereotactic ablative radiotherapy and surgery: two gold standards for early-stage non-small cell lung cancer? Ann Transl Med 2015;3(9):113. doi: 10.3978/j.issn.2305-5839.2015.05.08

Controversy and Debate

A pooled analysis of stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small cell lung cancer: is failure to recruit patients into randomized trials also an answer to the research question?

Carsten Nieder[1,2], Nicolaus H. Andratschke[3], Matthias Guckenberger[3]

[1]Department of Oncology and Palliative Medicine, Nordland Hospital, 8092 Bodø, Norway; [2]Institute of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, 9038 Tromsø, Norway; [3]Department of Radiation Oncology, University Hospital Zurich, 8091 Zurich, Switzerland
Correspondence to: Carsten Nieder, MD. Department of Oncology and Palliative Medicine, Nordland Hospital, 8092 Bodø, Norway. Email: carsten.nieder@nlsh.no.

Submitted Jun 01, 2015. Accepted for publication Jun 02, 2015.
doi: 10.3978/j.issn.2305-5839.2015.06.05
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.06.05

Non-small cell lung cancer (NSCLC) is among the most common cancers and biggest health care challenges in large parts of the world. Patients with locally advanced NSCLC comprise a heterogeneous group and many of them have unsatisfactory outcomes despite aggressive multimodal treatment approaches. Those with stage I disease (no distant or lymph node metastases; N0 M0) have the highest chance for cure. In the current classification system T-stage is based on primary tumor size (T1a max. 2.0 cm, T1b 2.1-3.0 cm, T2a 3.1-5.0 cm). Tumors larger than 5 cm are classified as stage II, even in the absence of lymph node metastases. In addition stage I requires that these tumors are surrounded by lung or visceral pleura and do not invade the main bronchus (1). Such tumors rarely cause any clinical symptoms, making early detection at this curable stage both challenging and crucial. Screening of high-risk patients using low-dose thoracic computed tomography (CT) imaging is therefore advocated (2).

The historical gold standard for treatment of stage I NSCLC, surgery with lobectomy and systematic hilar and mediastinal lymph node dissection as the sole curative approach, has recently been challenged by hypofractionated stereotactic ablative radiation therapy (SBRT or SABR), due to several reports describing high local control, low regional failure rates and good disease specific survival. SABR has evolved along the same principles that guided successful implementation of high-precision stereotactic radiotherapy for intracranial targets. Groups from Sweden and Japan, and later different European countries and the United States of America developed slightly different technical and planning approaches (3-6). A common feature was short overall treatment time, which is advantageous from a radiobiological point of view and convenient for patients. With the ability to deliver high biologically effective doses (BED) equivalent to more than 100 Gy in conventional 2-Gy fractions regardless of equipment and technique, local control rates rise considerably above those obtained in historical series, where conventional fractionated radiotherapy was administered over many weeks (7). Consequently, local progression as a major source of treatment failure does not limit survival after SABR. A recent multi-institutional analysis reported 2-year local recurrence (LR) of 4% after SBRT with BED >105 Gy as compared to 15% for <105 Gy (P<0.01) (8). Longer treatment duration (≥11 elapsed days) was associated with a 2-year LR of 14% *vs*. 4% for ≤10 days (P<0.01). After initial uncertainty about the safety of SABR in central tumors and prescription of relatively low equivalent doses, which resulted in sub-optimal LR, reluctance to treat to high BED has decreased and prospective studies have been designed (9).

When implementing SABR, for example, in two of the authors' previous departments in Munich and Wuerzburg, Germany, around the year 2000, referring physicians almost exclusively selected very old patients or those with serious comorbidity (10). In other words, most of the irradiated patients were not eligible for surgery and some not even

Table 1 Comparison between the two study arms

Characteristic	Study arm	
	SABR group	Surgery group
Number of patients	31	27
Stage		
T1a	52%	67%
T1b	35%	30%
T2a	13%	4%
Peripheral		
No	6%	11%
Yes	94%	89%

SABR, stereotactic ablative radiation therapy.

for invasive diagnosis, needed to obtain tissue and histology confirmation. Due to this selection bias, overall survival was not comparable to surgical series. Most patients died from cardiovascular and pulmonary comorbidity (as well as second primary cancers), not from the irradiated NSCLC. After a few years and due to the fact that very few patients relapsed, referral patterns changed towards a healthier population, also including occasional patients who refused surgery. All patients were discussed in multidisciplinary tumor boards.

Although initial studies on SABR were heterogeneous (comprised of both prospective and retrospective series with limited patients numbers, in part without histological confirmation of malignancy), the results prompted several phase II trials and later, population-based studies and propensity-matched analyses, which supported the concept of randomized phase III trials in early stage I NSCLC, comparing SABR to surgical resection in operable patients. The ambitious phase III trials (ACOSOG Z4099, ROSEL, STARS) were closed early because of slow accrual. However, ROSEL (a Dutch trial) and STARS (an international trial) shared similar entry criteria and study design, allowing for a pooled analysis. The latter has recently been reported and provides the best available evidence at this point in time (11).

Both randomized studies intended to compare overall survival of operable stage I NSCLC (T1-2a) treated with SABR or lobectomy. In principle, it makes sense to combine the small databases from both studies, which have insufficient statistical power on their own, in order to provide clinically applicable hints and hypotheses. In perspective, the failure to accrue patients resembles previous attempts to compare surgery and radiotherapy or chemoradiotherapy in other scenarios, such as bladder or prostate cancer. It is obviously not very appealing to patients and referring clinicians if the study arms provide extremely different treatment approaches, compared to for example studies where two different radiotherapy fractionation regimens or two different cytotoxic drug cocktails are tested.

The STARS trial attempted to include 420 patients, assuming 82% 3-year overall survival after surgery and a hazard ratio of less than 1.66. The inferiority limit for the ROSEL study was a hazard ratio of 1.35. In essence, the aim was to demonstrate that SABR would provide outcomes comparable to invasive treatment. After disappointing accrual in the time period 2008-2013 the study groups were left with 58 patients from both trials combined. Having said that combining both datasets makes sense from a statistical point of view (increased statistical power), one has to take a closer look at the details. What are the differences between the patients included in STARS and ROSEL, respectively? How cautiously should we interpret the results? As a matter of fact, stratification criteria differed between the studies. Patients without histological confirmation but fulfilling certain clinical criteria pointing strongly towards NSCLC were eligible for the ROSEL but not the STARS trial. Follow-up intervals were different (quite large time intervals of 6 months for 2 years, then annually in the STARS trial), raising the possibility that some of the STARS patients might have gone with undetected relapse at the time of analysis. The differences in equipment and radiotherapy details are probably less important, because sufficient doses were prescribed in both trials. STARS relied on CyberKnife equipment and implanted fiducial markers for image guidance. ROSEL utilized linear accelerators from multiple vendors. Three to five fractions were administered. It is also known from studies of stereotactic radiosurgery for brain metastases that equipment and methodology are not crucial determinants of outcome as long as the radiation dose is sufficiently high (12).

In both study arms median age was 67 years. Most patients had performance status 0 or 1. Other information is shown in *Table 1*. Comorbidity was not reported. Median follow-up was 40 months in the SABR group and 35 months in the surgery group. Median survival was not reached for either treatment group. Estimated survival favored the SABR group (95% at 3 years compared to 79% after surgery), P=0.037, hazard ratio 0.14 (95% confidence interval 0.017-1.19). Because of short follow-up relapse frequencies are preliminary. No significant differences emerged. Only one patient developed LR (treated with SABR, salvaged by lobectomy). Regional recurrence was

numerically higher in the SABR group (13% *vs*. 4%) without reaching statistical significance. Toxicity after SABR was in the expected range (max. grade III in 10% of the patients), including dyspnea, cough, fatigue, chest wall pain and one incidence of rib fracture. In the surgery group, one patient died of surgical complications and one developed grade IV dyspnea. Other adverse events included grade III dyspnea, infections, chest pain and others resulting in 44% of the surgical patients suffering from grade 3-4 treatment-related adverse events.

Since these results suggest that SABR is better tolerated and might lead to better survival, the authors correctly stated that SABR can be considered a treatment option in operable patients needing a lobectomy, and not only a compromise for those the surgeons wont touch. The equipoise suggested by the combined analysis of STARS and ROSEL justifies efforts for additional randomized trials. The latter would be desirable because of the small patient numbers and limited follow-up. In reality it is difficult to expect better recruitment in the future. The present results will definitely not diminish bias and stimulate patients' interest in surgery. It required tremendous effort to prepare the study protocols and provide the available data from STARS and ROSEL. Unfortunately, recruitment was slow and the conclusions therefore weaker than anticipated. While highly effective local treatment for small stage I NSCLC has become reality, challenges persist regarding control of larger tumors with SABR. Maybe combined modality treatment will contribute to improved outcomes, paralleling the developments in stage III disease. Many patients with lung cancer ultimately die from distant metastases and therefore, better understanding of the processes leading to tumor cell seeding and more effective approaches to control metastatic disease are needed. Preliminary evidence suggests that combinations of systemic and local therapy including SABR should be studied in well-designed, sufficiently powered trials, unless widespread disease precludes reasonable target volumes (13-16).

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2:706-14.
2. Christensen JD, Chiles C. Low-Dose Computed Tomographic Screening for Lung Cancer. Clin Chest Med 2015;36:147-60.
3. Blomgren H, Lax I, Näslund I, et al. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 1995;34:861-70.
4. Uematsu M, Shioda A, Tahara K, et al. Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience. Cancer 1998;82:1062-70.
5. Wulf J, Hädinger U, Oppitz U, et al. Stereotactic radiotherapy of targets in the lung and liver. Strahlenther Onkol 2001;177:645-55.
6. Timmerman R, Papiez L, Suntharalingam M. Extracranial stereotactic radiation delivery: expansion of technology beyond the brain. Technol Cancer Res Treat 2003;2:153-60.
7. Rowell NP, Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable). Cochrane Database Syst Rev 2001;(2):CD002935.
8. Kestin L, Grills I, Guckenberger M, et al. Dose-response relationship with clinical outcome for lung stereotactic body radiotherapy (SBRT) delivered via online image guidance. Radiother Oncol 2014;110:499-504.
9. Adebahr S, Collette S, Shash E, et al. LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective. Br J Radiol 2015;88:20150036.
10. Andratschke N, Zimmermann F, Boehm E, et al. Stereotactic radiotherapy of histologically proven inoperable stage I non-small cell lung cancer: patterns of failure. Radiother Oncol 2011;101:245-9.
11. 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.
12. Nieder C, Grosu AL, Gaspar LE. Stereotactic radiosurgery (SRS) for brain metastases: a systematic review. Radiat Oncol 2014;9:155.
13. Nieder C, Tollåli T, Reigstad A, et al. Oligometastatic non-small cell lung cancer: a significant entity outside of specialized cancer centers? Med Princ Pract 2014;23:526-31.
14. Ashworth A, Rodrigues G, Boldt G, et al. Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature. Lung Cancer

2013;82:197-203.
15. Griffioen GH, Toguri D, Dahele M, et al. Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): patient outcomes and prognostic factors. Lung Cancer 2013;82:95-102.
16. De Ruysscher D, Wanders R, van Baardwijk A, et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). J Thorac Oncol 2012;7:1547-55.

Cite this article as: Nieder C, Andratschke NH, Guckenberger M. A pooled analysis of stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small cell lung cancer: is failure to recruit patients into randomized trials also an answer to the research question? Ann Transl Med 2015;3(11):148. doi: 10.3978/j.issn.2305-5839.2015.06.05

Controversy and Debate

The radiobiological targets of SBRT: tumor cells or endothelial cells?

Sana D. Karam, Shilpa Bhatia

Department of Radiation Oncology, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO 80045, USA
Correspondence to: Sana D. Karam, MD, PhD. Department of Radiation Oncology, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO 80045, USA. Email: sana.karam@ucdenver.edu.

Abstract: The development of stereotactic body radiation therapy (SBRT) and stereotactic radiosurgery (SRS) techniques has revolutionized the practice of radiation oncology. The radiobiological targets that alter the therapeutic response to SBRT remain a subject of debate. The prevailing perspective has been that the radiation-induced damage to endothelial cells and changes in microvasculature facilitate tumor response to SBRT. A provocative study by Moding *et al*. (PMID: 25761890), challenged this notion by elucidating the role of tumor cells versus endothelial cells in mediating sarcoma eradication following high-dose SBRT. Using dual recombinase technology, they generated primary sarcomas in genetically engineered mouse models (GEMMs). They also modulated the apoptotic pathway and radiosensitization profile using targeted mutations in either tumor cells or endothelial cells. Unlike transplanted tumor models, the findings here suggest that deletion of the pro-apoptotic gene *Bax* or of the DNA-damage response gene *ATM* in endothelial cells did not result in tumor eradication to high dose SBRT, despite extensive endothelial cell death. On the other hand, genetic targeting of *ATM* gene in tumor cells achieved local sarcoma control and tumor eradication. These findings imply that tumor cells rather than endothelial cells act as prime targets affecting a tumor eradication response to SBRT. The translational implications of these findings are of great potential significance. When targeting endothelial cells, delivery of SBRT irradiation can only result in tumor growth delay. The benefit of targeting *ATM* in this setting will be radiation dose dependent. Curative intent, tumor eradication and local control, on the other hand, are only possible by targeting tumor cells with high dose SBRT (50 Gy in 1 fraction) and with radiosensitization by *ATM* deletion. In the absence of radiosensitization, only palliation is possible with high dose SBRT. Whether these provocative findings can be extrapolated to other translational tumor models or proved valid in clinical trials remains the subject of future studies. The mechanisms by which tumors compensate to SBRT's endothelial cell damage, such as new vascular recruitment, and/or recruitment of other immune and stromal components, are also critical questions for the field of radiobiology to address. Such mechanistic understanding of the key cellular players mediating SBRT response in a model system that recapitulates human disease will be essential in designing targeted radiosensitizers ultimately aimed at improving the therapeutic ratio.

Keywords: Stereotactic body radiation therapy (SBRT); stereotactic ablative radiotherapy; stereotactic radiosurgery (SRS); dose; hypofractionated; radiosensitization; endothelial cell death; *ATM*

Submitted Aug 26, 2015. Accepted for publication Aug 31, 2015.
doi: 10.3978/j.issn.2305-5839.2015.09.17
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.09.17

Remarkable advances in the field of medicine and imaging diagnostics have led to the emergence of such techniques as stereotactic body radiation therapy (SBRT) and stereotactic radiosurgery (SRS). The advent of SBRT and SRS has brought a paradigm shift in the field of radiation therapy practice. Typically, with SRS and SBRT, cancer patients can now be effectively treated with a small number of high radiation doses. Dramatic improvements in tumor control have been achieved in several clinical studies following high-dose radiation therapy (1). However, the success of SBRT

has raised questions with regard to the radiobiological targets affecting tumor response following high-dose radiation therapy. The efficacy of SBRT irradiation in the curative setting also remains a question of significant clinical interest.

An elegant study by Moding *et al*., recently published in *Science Translational Medicine*, challenged the prevailing hypothesis that endothelial cells act as main contributors to radiation response in a sarcomatous mouse model (2). Their data provide provocative evidence supportive of a model whereby tumor cells, rather than endothelial cells, mediate SBRT cell killing of sarcomatous tumors (2). They also underscore the importance of using radiosensitizers in combination with high dose SBRT radiation for curative tumor eradication.

It has been well documented that a tumor microenvironment comprised of extracellular matrix, carcinoma-associated fibroblasts, immune cells, and endothelial cells plays a critical role in tumor initiation, progression, and metastatic spread (3). Changes in the tumor microenvironment also could have a marked impact on the therapeutic response in tumor cells (4,5). However, our understanding of the response of the tumor microenvironment, including the fate of microvasculature to high-dose SBRT, is still rudimentary. For a long time, the prevailing perspective in the field of radiation biology was that the ultimate outcome of SRS/SBRT is largely governed by radiation-induced damage inflicted on the endothelial cells and tumor vasculature (4,5). However, studies in the field of radiation biology have advanced our current knowledge, and alternate theories have emerged.

The study by Moding *et al*. used an ingenious dual recombinase technology to generate primary sarcomas in genetically engineered mouse models (GEMMs) with selective mutations in either tumor cells or endothelial cells (2). The remarkable use of GEMMs allowed for tumor formation in the native environment in immunocompetent mice. Unlike transplanted tumor models, GEMMs preserve the tumor stroma and microenvironment of human cancers more faithfully and can be advantageous in predicting the therapeutic response.

Since previous reports suggested that endothelial cell death and microvascular damage played a role in tumor control following radiation therapy (4,6,7), the authors mutated the proapoptotic gene *Bax* in endothelial cells of GEMMs. They observed that *Bax* deletion in endothelial cells did not enhance radiation-induced endothelial cell apoptosis or, more importantly, tumor response to SBRT (2).

Perhaps more intriguing was the ultimate lack of effect on local *in vivo* tumor control in their model system when altering the radiosensitization profile of endothelial cells, despite evidence of induction of cell death. They showed that targeted deletion of the *ATM* gene, a master regulator of DNA damage response pathway (8), in endothelial cells resulted in increased cell death following high-dose SBRT (2). However, this failed to translate into *in vivo* difference in tumor eradication (failure to triple in size after 18 weeks of radiation treatment) or local control (absence of tumor volume tripling) outcomes between the animals where endothelial cells were *ATM* deleted versus the control group. The same finding was observed with a single high SBRT dose of 50 Gy in one fraction or with hypofractionated SBRT dose of 20 Gy in 4 fractions.

To appreciate this finding, one has to examine the earlier work of Moding and colleagues using different dosing and fractionation regimens (9). They showed that if endothelial cells are targeted at SBRT dosing of 20 Gy or a more conventional fractionation of 30 Gy in 10 fractions, improved tumor growth delay (55% longer time to tripling in size) is seen if radiosensitization is employed through *ATM* gene deletion (9).

The above findings suggest a distinction between tumor eradication and tumor growth delay upon targeting endothelial cells and highlight the importance of radiation dose and of using radiosensitizers. Importantly, they carry potentially translational significance, particularly given that targeting endothelial cells with anti-angiogenic agents such as VEGF inhibitors is not uncommon. Targeting endothelial cells is never curative, as it will not eradicate sarcomas even if *ATM* deletion is present. However, if palliation or growth delay is the intent of treatment, then targeting endothelial cells will be of benefit. Whether or not radiosensitization (*ATM* deletion) is necessary in palliative treatment when endothelial cells are targeted will simply depend on the radiation dose being used. At dosing of 20 Gy in a single fraction or at conventional fractionation of 30 Gy in 10 fractions, radiosensitization by targeting *ATM* would be necessary. However, at dosing of 50 Gy in a single fraction or 20 Gy in 4 fractions, targeting *ATM* in endothelial cells will not add any more benefit.

Strikingly different results were obtained in tumor cells. Specifically, Moding and colleagues showed that altering the radiosensitization profile by targeted *ATM* deletion in tumor cells resulted in a significant tumor eradication following high-dose SBRT (2). This was evident both in the *in vitro* and the *in vivo* model systems used in this study. Without radiosensitization and in the control group, only tumor growth delay in response to 50 Gy can be observed.

Two provocative findings are generated from these results. First, it is tumor cells rather than endothelial cells that act as important targets mediating sarcoma eradication by SBRT (2). Second, and equally important, tumor eradication in the high dose SBRT setting is only achieved in combination with radiosensitizers such as *ATM* inhibitors (2).

This is provocative as, for example, up to one third of patients with medically inoperable early stage lung cancer are treated with high dose SBRT per practice guidelines (10). Similarly, in the treatment of solitary or oligometastasis, high dose SBRT is used in the absence of radiosensitizers (11). The results by Moding and colleagues, as they aptly note out in their discussion, are limited to sarcomas, and the biological effects of high-dose SBRT may vary based on tumor type or target tissue (2). It nevertheless raises the question of whether better clinical outcomes would be achieved if high dose SBRT were coupled with radiosensitizers in other tumor models.

Whether altering the radiosensitization profile in sarcoma cells by methods other than *ATM* deletion or other non-DNA repair pathways would have resulted in tumor eradication remains to be shown. It would have been interesting for the authors, for example, to examine whether targeting *Bax* in sarcoma cells would have had a similar effect on local control as that observed with *ATM* deletion. When the pharmacological inhibitor of *ATM* was used, a significant increase in TUNEL staining was observed, suggesting increased cell death (2). Translationally, it would be important to determine whether combining the targeting of the apoptotic pathway with high dose SBRT would have resulted in tumor eradication.

Multiple theories exist for compensatory responses negating the effect of endothelial cell damage on tumor control, some of which were discussed in the manuscript. These are imperative, as they shed light on potential combination therapies that could improve local control to SBRT by overcoming compensatory responses to endothelial cell damage. The contribution of other stromal cell population might be one responsible mechanism for tumor relapse following high-dose radiation therapy. Strong evidence suggests that immune cell components plays a role in mediating anti-tumorigenic effects in response to SBRT (12). This theory is supported by the generation of a tumor microenvironment that can elicit an immunological response (1,7). Thus, to uncover the immune aspects of SBRT-mediated killing of tumor cells, it would be important to target the immune cells and determine the effects in response to high-dose SBRT.

Similarly, revascularization of tumors following radiation therapy from outside the radiation field is another factor that could explain sarcoma recurrence despite high dose SBRT. In an earlier study, Moding and colleagues (9) validated that endothelial cell death that accompanies radiosensitization mediated by *ATM* deletion, translated into a functional change in the vasculature in the irradiation field 24 h following treatment with a single 20 Gy dose. One can assume that, at the curative 50 Gy (or 20 Gy in 4) dosing reported in this manuscript (2), similar revascularization is present within the radiation field when radiosensitization is utilized. In mice where tumors recurred despite endothelial cell death and radiosensitization, the source of neovessels in relapsing tumors could be surviving endothelial cells still capable of establishing a tumor vasculature during post-radiation recurrence (13). This, however, is unlikely, given the high curative dosing used here. Whether recruitment of "distal" stroma from outside the field in the form of inflammatory bone marrow-derived cells (13) plays a role in this context remains a subject for future study.

Cancer stem cell clearance could also be a pivotal factor contributing to the tumor response following SBRT (7) that could negate any effect of endothelial cell damage. Cancer stem cells have been shown to occupy the perivascular niche in tumors (12). These cells display an increased activation of AKT/mTOR pathway regulating cell proliferation and cell survival (12). Previous studies have reported that these cancer stem cells confer radioresistant characteristics and might be responsible for tumor recurrence following fractionated radiotherapy (7,12). Following a low dose of radiation (2 Gy), these perivascular cells show cell cycle arrest within 6 hours of irradiation but re-enter cell cycle and start proliferating in 72 h, ultimately affecting the treatment response (7). Thus, one of the implications of high-dose SBRT could be the ablation of this self-renewing population of radioresistant cancer stem cells, leading to tumor growth eradication (7).

The clinical applicability of the findings shown in this manuscript will be limited largely by concern over radiosensitization of normal tissues by direct targeting of *ATM*. When pharmacological inhibition of *ATM* was used following whole heart irradiation, they showed that radiosensitization there is far less impressive than it is in sarcoma cells (2). It is important to note, though, that the dose there was only 20 Gy in a single fraction and not the "curative" 50 Gy in a single fraction. A single dose of 20 Gy, however, only resulted in growth delay, not tumor eradication, despite the presence of pharmacological inhibitor of *ATM*. Similarly, they showed in their earlier work that

ATM deletion does not radiosensitize heart cells at 20 Gy in a single fraction (9). For radiosensitization to occur with *ATM*, the cells have to be proliferating and progressing through the cell cycle (9). In other words, loss of *ATM* does not affect all tissues equally. At doses of 50 Gy in a single fraction required for tumor eradication, the therapeutic index would therefore be largely determined by the volume of tumor and proximity to critical structures, particularly proliferative, non-quiescent tissue. The requirement of such a high dose of 50 Gy in single fraction or 80 Gy in four fractions in combination with *ATM* targeting would likely be prohibitive in the clinical setting. Testing the benefit of other radiosensitizers that may not be as prevalent in normal tissue in a similarly elegant manner would be of clinical importance.

In short, the findings documented by Moding *et al.* (2) have challenged a fundamental assumption of SBRT radiobiology. The mechanistic understanding provided by using such systems as GEMMs, which better recapitulates human disease, allows for designing future studies aimed at improving tumor control outcomes. Studying key compensatory mechanisms that could explain the inherent lack of tumor control when endothelial cells are targeted with high dose SBRT will be critical for developing better therapeutic strategies. Immunotherapy, blockade of tumor-promoting effects of TGF-β, and targeting tumor revascularization from outside the radiation field could provide potential therapeutic benefit when combined with radiosensitizers and high dose SBRT. Finally, this study challenges the current practice of using high dose SBRT alone in a curative intent setting without radiosensitizers. Future studies in other tumor models aimed at expanding the generalizability of these findings into translational models, particularly those where high dose SBRT remains the standard of care, are warranted.

Acknowledgements

Dr. Karam is funded by Paul Calabresi Career Development Award for Clinical Oncology (K12), American Cancer Society Institutional Grant (ACSIG), Cancer League of Colorado.

Footnote

Provenance: This is a Guest Editorial commissioned by the Section Editor Hui Kong, MD, PhD (Department of Respiratory Medicine, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

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

References

1. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? Int J Radiat Oncol Biol Phys 2014;88:254-62.
2. Moding EJ, Castle KD, Perez BA, et al. Tumor cells, but not endothelial cells, mediate eradication of primary sarcomas by stereotactic body radiation therapy. Sci Transl Med 2015;7:278ra34.
3. Chen F, Zhuang X, Lin L, et al. New horizons in tumor microenvironment biology: challenges and opportunities. BMC Med 2015;13:45.
4. Garcia-Barros M, Paris F, Cordon-Cardo C, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science 2003;300:1155-9.
5. Fuks Z, Kolesnick R. Engaging the vascular component of the tumor response. Cancer Cell 2005;8:89-91.
6. Kolesnick R, Fuks Z. Radiation and ceramide-induced apoptosis. Oncogene 2003;22:5897-906.
7. Park HJ, Griffin RJ, Hui S, et al. Radiation-induced vascular damage in tumors: implications of vascular damage in ablative hypofractionated radiotherapy (SBRT and SRS). Radiat Res 2012;177:311-27.
8. Paull TT. Mechanisms of ATM Activation. Annu Rev Biochem 2015;84:711-38.
9. Moding EJ, Lee CL, Castle KD, et al. Atm deletion with dual recombinase technology preferentially radiosensitizes tumor endothelium. J Clin Invest 2014;124:3325-38.
10. 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.
11. Videtic GM. The role of stereotactic radiotherapy in the treatment of oligometastases. Curr Oncol Rep 2014;16:391.
12. Brown JM, Koong AC. High-dose single-fraction radiotherapy: exploiting a new biology? Int J Radiat Oncol Biol Phys 2008;71:324-5.
13. Kozin SV, Duda DG, Munn LL, et al. Neovascularization after irradiation: what is the source of newly formed vessels in recurring tumors? J Natl Cancer Inst 2012;104:899-905.

Cite this article as: Karam SD, Bhatia S. The radiobiological targets of SBRT: tumor cells or endothelial cells? Ann Transl Med 2015;3(19):290. doi: 10.3978/j.issn.2305-5839.2015.09.17

Controversy and Debate

Stereotactic ablative body radiotherapy (SABR): an alternative to surgery in stage I-II non-small-cell cancer of the lung?

René-Olivier Mirimanoff

Department of Radiation Oncology, Clinique de La Source, Lausanne CH-1004, Switzerland
Correspondence to: René-Olivier Mirimanoff, MD. Clinique de La Source (CLS), Avenue Vinet 30, CH-1004 Lausanne, Switzerland.
Email: rene-olivier.mirimanoff@chuv.ch.

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 control and toxicity will be reviewed, and an attempt will be made to compare the results of SABR with those of surgery.

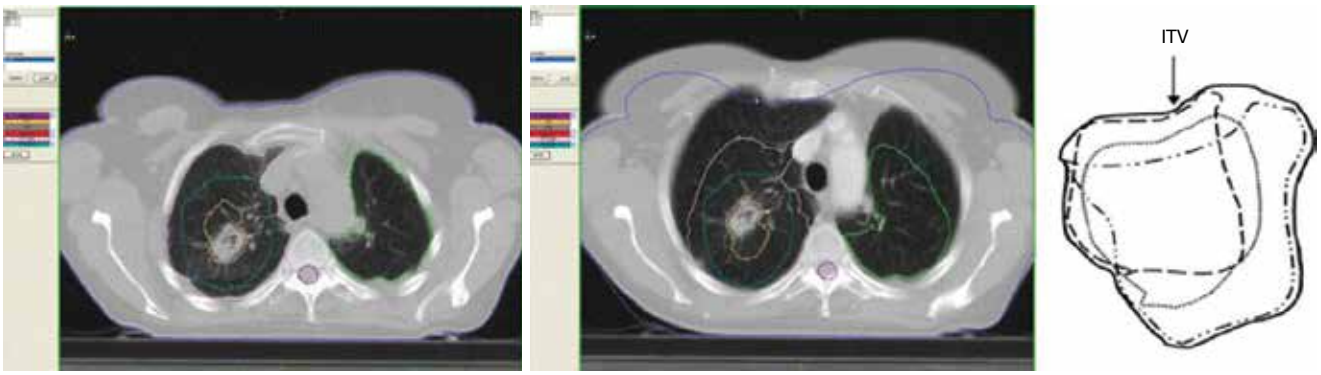


Figure 1 Schematic representation of an internal target volume (ITV) with comparative CT scans of the same patient in expiration and inspiration, and treated at our institution (CLS) (courtesy Mrs Bressan RTT, CLS).

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 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

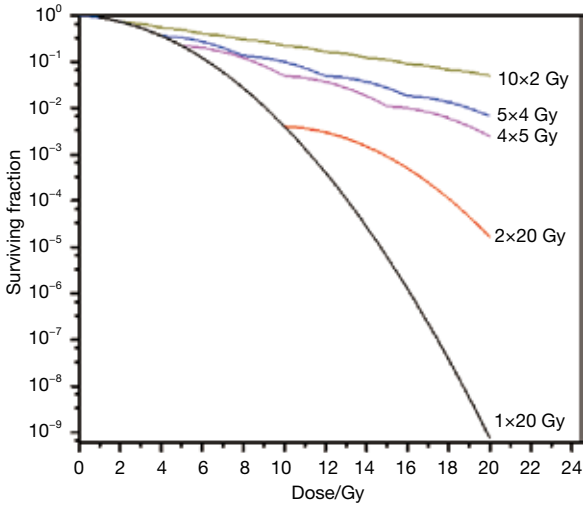


Figure 2 Cell survival curves with various fractionation schedules for a total dose of 20 Gy. Note the largely different cell kill between 20 Gy given in one fraction versus 20 Gy given in 10 fractions.

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*). 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

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.

calculation formulae can be used, like the BED equation, where (3,10):

$$BED = D\left(1 + d/\alpha/\beta\right),$$

where BED = biologically equibalent dose;

D = total dose in Gy;

d = dose perfraction 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 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

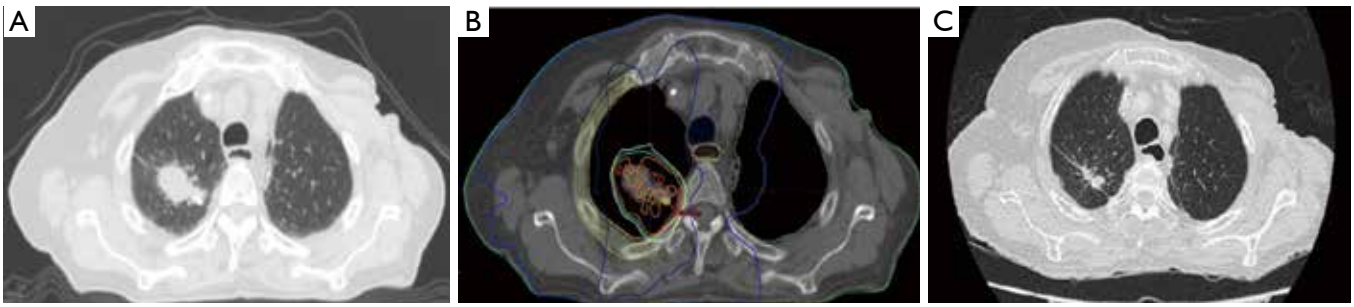


Figure 3 CT scan of a 80-year-old patient treated at our institution (CLS) for a right upper lobe NSCLC (A). He received a SABR of 60 Gy in 5 fractions with a V-MAT technique (B). CT scan at 6 months shows some residual opacity secondary to the treatment (C).

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.

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 Senthi *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 recurrence rate of 4.9%, 7.8%, and 14.7%, respectively, and

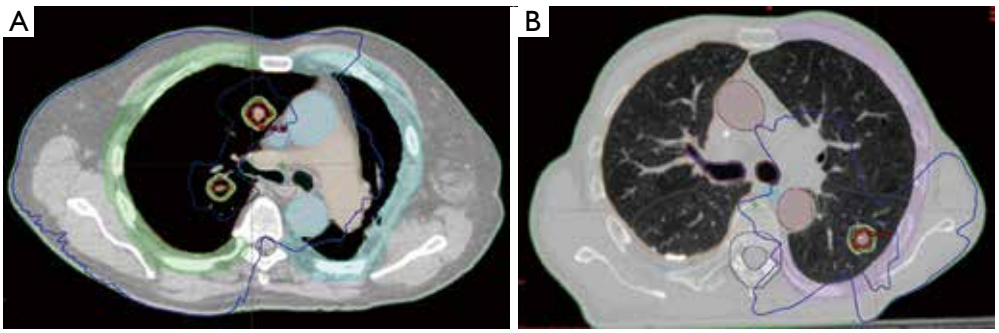


Figure 4 Example of two different patients treated at our institution (CLS) with stereotactic ablative body radiotherapy (SABR). (A) This patient received for two central lesions a dose of 60 Gy in 8 fractions of 7.5 Gy (BED10: 105); (B) the second patient received for a left upper lobe lesion a dose of 60 Gy in 5 fractions of 12 Gy (BED10: 132).

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-oesophagial fistulae, brocho-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 compromizing 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. Senthi *et al.* have reviewed the toxicity of SABR based on 20 publications including 563 central lung tumors (5). They confirm that with the above-mentionned 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 co-morbidities and inacceptable 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. Verstegen *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. Verstegen *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.

References

1. Scott WJ, Howington J, Feigenberg S, et al. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:234S-242S.
2. Schulte T, Schniewind B, Dohrmann P, et al. The extent of lung parenchyma resection significantly impacts long-term quality of life in patients with non-small cell lung cancer. Chest 2009;135:322-9.
3. Rueth NM, Parsons HM, Habermann EB, et al. Surgical treatment of lung cancer: predicting postoperative morbidity in the elderly population. J Thorac Cardiovasc Surg 2012;143:1314-23.
4. Haasbeek CJ, Palma D, Visser O, et al. Early-stage lung cancer in elderly patients: a population-based study of changes in treatment patterns and survival in the Netherlands. Ann Oncol 2012;23:2743-7.
5. Senthi S, Haasbeek CJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol 2013;106:276-82.
6. Palma DA, Senan S. Improving outcomes for high-risk patients with early-stage non-small-cell lung cancer: insights from population-based data and the role of stereotactic ablative radiotherapy. Clin Lung Cancer 2013;14:1-5.
7. Senan S, Paul MA, Lagerwaard FJ. Treatment of early-stage lung cancer detected by screening: surgery or stereotactic ablative radiotherapy? Lancet Oncol 2013;14:e270-4.
8. Boujelbene N, Elloumi F, Kamel ME, et al. Stereotactic body radiation therapy in stage I inoperable lung cancer: from palliative to curative options. Swiss Med Wkly 2013;143:w13780.
9. Louie AV, Palma DA, Dahele M, et al. Management of early-stage non-small cell lung cancer using stereotactic ablative radiotherapy: controversies, insights, and changing horizons. Radiother Oncol 2015;114:138-47.
10. Dosoretz DE, Katin MJ, Blitzer PH, et al. Radiation therapy in the management of medically inoperable carcinoma of the lung: results and implications for future treatment strategies. Int J Radiat Oncol Biol Phys 1992;24:3-9.
11. Wisnivesky JP, Bonomi M, Henschke C, et al. Radiation therapy for the treatment of unresected stage I-II non-small cell lung cancer. Chest 2005;128:1461-7.
12. Kushnirsky M, Patil V, Schulder M. The history of stereotactic radiosurgery. In: Chin LS, Ragine WR, editors. Principles and practice of stereotactic radiosurgery. Springer, 2015:3-10.
13. Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. Semin Radiat Oncol 2008;18:215-22.
14. Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. J Clin Oncol 2014;32:2847-54.
15. Bradley J. Radiographic response and clinical toxicity following SBRT for stage I lung cancer. J Thorac Oncol 2007;2:S118-24.
16. Senthi S, Dahele M, van de Ven PM, et al. Late radiologic changes after stereotactic ablative radiotherapy for early stage lung cancer: a comparison of fixed-beam versus arc delivery techniques. Radiother Oncol 2013;109:77-81.
17. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004;101:1623-31.
18. Xia T, Li H, Sun Q, et al. Promising clinical outcome of stereotactic body radiation therapy for patients with inoperable Stage I/II non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006;66:117-25.
19. Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;70:685-92.
20. Chen Y, Guo W, Lu Y, et al. Dose-individualized stereotactic body radiotherapy for T1-3N0 non-small cell lung cancer: long-term results and efficacy of adjuvant chemotherapy. Radiother Oncol 2008;88:351-8.

21. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.
22. Bradley JD, El Naqa I, Drzymala RE, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung cancer: the pattern of failure is distant. Int J Radiat Oncol Biol Phys 2010;77:1146-50.
23. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
24. Ricardi U, Filippi AR, Guarneri A, et al. Stereotactic body radiation therapy for early stage non-small cell lung cancer: results of a prospective trial. Lung Cancer 2010;68:72-7.
25. Matsuo Y, Shibuya K, Nagata Y, et al. Prognostic factors in stereotactic body radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2011;79:1104-11.
26. Widder J, Postmus D, Ubbels JF, et al. Survival and quality of life after stereotactic or 3D-conformal radiotherapy for inoperable early-stage lung cancer. Int J Radiat Oncol Biol Phys 2011;81:e291-7.
27. Takeda A, Kunieda E, Sanuki N, et al. Stereotactic body radiotherapy (SBRT) for solitary pulmonary nodules clinically diagnosed as lung cancer with no pathological confirmation: comparison with non-small-cell lung cancer. Lung Cancer 2012;77:77-82.
28. Shibamoto Y, Hashizume C, Baba F, et al. Stereotactic body radiotherapy using a radiobiology-based regimen for stage I nonsmall cell lung cancer: a multicenter study. Cancer 2012;118:2078-84.
29. Taremi M, Hope A, Dahele M, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. Int J Radiat Oncol Biol Phys 2012;82:967-73.
30. Hamamoto Y, Kataoka M, Yamashita M, et al. Factors affecting the local control of stereotactic body radiotherapy for lung tumors including primary lung cancer and metastatic lung tumors. Jpn J Radiol 2012;30:430-4.
31. Crabtree TD, Puri V, Robinson C, et al. Analysis of first recurrence and survival in patients with stage I non-small cell lung cancer treated with surgical resection or stereotactic radiation therapy. J Thorac Cardiovasc Surg 2014;147:1183-1191; discussion 1191-2.
32. Kestin L, Grills I, Guckenberger M, et al. Dose-response relationship with clinical outcome for lung stereotactic body radiotherapy (SBRT) delivered via online image guidance. Radiother Oncol 2014;110:499-504.
33. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 2003;124:1946-55.
34. Chi A, Tom55.a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 2003;124:1946-55.;124:1946-55.3;124:1946-55.124:1946-55.6-55.5.l Clin Oncol 2011;34:432-41.
35. Zhang J, Yang F, Li B, et al. Which is the optimal biologically effective dose of stereotactic body radiotherapy for Stage I non-small-cell lung cancer? A meta-analysis. Int J Radiat Oncol Biol Phys 2011;81:e305-16.
36. van Baardwijk A, Tomjk A, TommElmpt W, et al. Is high-dose stereotactic body radiotherapy (SBRT) for stage I non-small cell lung cancer (NSCLC) overkill? A systematic review. Radiother Oncol 2012;105:145-9.
37. Chi A, Liao Z, Nguyen NP, et al. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: clinical implications. Radiother Oncol 2010;94:1-11.
38. Senthi S, Lagerwaard FJ, Haasbeek CJ, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol 2012;13:802-9.
39. Thibault I, Chiang A, Erler D, et al. Predictors of Chest Wall Toxicity after Lung Stereotactic Ablative Radiotherapy. Clin Oncol (R Coll Radiol) 2015. [Epub ahead of print].
40. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
41. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:348-53.
42. Verstegen NE, Lagerwaard FJ, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy following a clinical diagnosis of stage I NSCLC: comparison with a contemporaneous cohort with pathologically proven disease. Radiother Oncol 2011;101:250-4.
43. Moghanaki D, Karas T. Surgery versus SABR for NSCLC. Lancet Oncol 2013;14:e490-1.
44. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage

I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 2013;24:1543-8.
45. Zhang B, Zhu F, Ma X, et al. Matched-pair comparisons of stereotactic body radiotherapy (SBRT) versus surgery for the treatment of early stage non-small cell lung cancer: a systematic review and meta-analysis. Radiother Oncol 2014;112:250-5.
46. Solda: F, Lodge M, Ashley S, et al. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic review and comparison with a surgical cohort. Radiother Oncol 2013;109:1-7.
47. Louie AV, Haasbeek CJ, Mokhles S, et al. Predicting Overall Survival After Stereotactic Ablative Radiation Therapy in Early-Stage Lung Cancer: Development and External Validation of the Amsterdam Prognostic Model. Int J Radiat Oncol Biol Phys 2015;93:82-90.
48. Brada M, Pope A, Baumann M. SABR in NSCLC--the beginning of the end or the end of the beginning? Radiother Oncol 2015;114:135-7.

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

Controversy and Debate

Pros: should a medically inoperable patient with a T2N0M0 non-small cell lung cancer central in the lung hilus be treated using stereotactic body radiotherapy?

Katrina Woodford, Sashendra Senthi

William Buckland Radiotherapy Centre, The Alfred, Australia

Correspondence to: Katrina Woodford. William Buckland Radiotherapy Centre, The Alfred, Australia. Email: katrina.woodford@wbrc.org.au; Sashendra Senthi. William Buckland Radiotherapy Centre, The Alfred, Australia. Email: S.Senthi@alfred.org.au.

Submitted Jun 08, 2015. Accepted for publication Aug 11, 2015.
doi: 10.3978/j.issn.2218-6751.2015.08.08
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2015.08.08

Introduction

The view that surgery represents the only curative treatment for non-small cell lung cancer (NSCLC) still prevails today. Perhaps the greatest achievement of stereotactic body radiotherapy (SBRT) has been to challenge this, providing a platform to promote radiotherapy as an effective curative treatment that should be considered alongside surgery (1). The impact of this is clearest when considering population-based outcomes from national cancer registries. In the Netherlands, the widespread implementation of SBRT has increased radiotherapy utilization, decreased the proportion of patients left untreated and as a consequence improved NSCLC survival (2). The logistic benefits of SBRT courses over conventional radiotherapy has clearly played a role in this, providing a treatment option for the elderly or those with significant comorbidities who might not otherwise be offered curative treatment. These patients represent the fastest growing population of lung cancer patients (3) and a proportion will have central tumors for which conventional radiotherapy is infeasible. The primary argument as to whether to use SBRT for central tumors rests with maintaining population survival gains and weighing the risks of harm against those of not offering curative treatment.

Why are there concerns using SBRT for central tumors and should there be?

It is clear that SBRT for central tumors represents a higher risk clinical scenario, with little prospective evidence compared to SBRT for peripheral tumors (4). Toxicity concerns first came to light when Timmerman defined 'central' and found SBRT for lesions within 2 cm of the bifurcation of lobar bronchi were 11 times more likely to result in severe toxicity, including death (5). However one needs to consider the limitations of applying such data to SBRT treatments delivered almost 10 years go. In the Timmerman report, SBRT occurred without 4DCT simulation, inhomogeneity-corrected dose calculation or daily soft-tissue based image guidance. Independently each of these factors may contribute to an increased risk of toxicity. The radiotherapy dose of 66 Gy in 3 fractions (used for T2 tumors) significantly exceeds that which is routinely used today or that is required for optimal local control (4). In addition to this, the scoring of toxicities may have overestimated the risk of death. Four of the six potentially 'SBRT-related' deaths were due to bacterial pneumonia, a common occurrence in a population with a median age of 70 years, an FEV1 less than 40% predicted and a smoking history of at least 20 pack years with frequent continued smoking. Concerns regarding the use of SBRT for central tumors were again brought to the fore when the *New England Journal of Medicine* reported a case of fatal airway necrosis using 50 Gy in 5 fractions with modern SBRT techniques (6). The report is important in that it highlights that death is possible and caution is required, but as with any case series, it provides no insight into the relative risk compared to treating peripheral tumors. The weight of such evidence, an unplanned subgroup analysis and case report, needs to be placed into context and have clinicians ask; does this justify denying my patient potentially curative treatment, when SBRT represents their only option.

Is there evidence to support using SBRT for central tumors?

There are limited prospective reports of SBRT outcomes for central tumors. Xia *et al*. reported outcomes for nine central tumors using an SBRT schedule of 50 Gy in 10 fractions delivered by gamma-knife system (7). Local control at 3 years was 93% (entire stage II cohort) and central tumors did not result in any grade 3 or higher toxicities. After longer follow-up, the 22 patients with central tumors Fakiris *et al*. originally reported on were found to have an overall survival and severe (grade 3-5) toxicity risk that was the same as that of peripheral tumors (8). Bral *et al*. reported on a prospective cohort of 40 patients, 17 of which were central tumors and treated to 60 Gy in 4 fractions (9). They found tumor location did not predict local control, patterns of relapse or overall survival. Although they found 20% of patients developed grade 3 pulmonary toxicity, and this was associated with central location (P=0.06) and PTV size >65 cc (P=0.02), central tumors were significantly larger than those peripherally located on average (67 *vs.* 42 cc, P=0.0009). Taremi *et al*. prospectively assessed 108 patients, 20 of which had central tumors. Although they did not assess the impact of tumor location on toxicity, they reported no grade 4 or 5 events (10). Videtic *et al*. prospectively investigated quality of life after SBRT in 21 patients, including 12 with central tumors treated with 50 Gy in 5 or 10 fractions (11). They found no grade 3 or higher toxicity or change in global quality of life and these did not correlate with tumor location.

When faced with elderly patients with central NSCLC, the majority of clinicians already feel there is sufficient evidence to utilize SBRT. A recent pattern of care study found more than 80% would use SBRT, the vast majority outside a clinical trial protocol, even if conventional radiotherapy was an option (12). The consequence of this has been increasingly robust retrospective evidence to support the use of SBRT. A recent systematic review found 20 reports of outcomes in more than 500 central tumors following SBRT (4). None of the included studies found central location predicted worse survival. In addition, SBRT related mortality was found to be dose-related, with a 2.8% (16/563) risk overall and a 1.0% (2/204) risk when an SBRT schedule with a BED_3 <210 Gy was utilized. This approximates to dose fractionations of 50 Gy in 5 factions or 60 Gy in 8 fractions. Since then, Mangona *et al*. identified 79 patients with central tumors and matched them to 79 patients with peripheral tumors (13). When baseline differences were accounted for using propensity-matched analysis, central tumors had the same toxicity profile as those peripherally located, with respective grade 3 or higher toxicities of 3% *vs.* 7% (P=0.48). Using a SBRT scheme of 48 Gy in 4 fractions for tumors <3 cm, 60 Gy in 5 fractions for tumors >3 cm and respecting their institutional organ at risk constraints (which were published), the 2-year incidence of grade 4 and 5 toxicity was <1%. Furthermore, Park *et al*. used logistic regression modeling in a cohort of 111 central and 140 peripheral NSCLC with a median follow-up of 31 months (14). On multivariate analysis tumor location did not impact survival, local control or toxicity.

Putting risks into context and patient-centeredness

As surgery is regarded to be the standard of care treatment for NSCLC, the mortality following lung cancer surgery can be considered the accepted benchmark against which to consider SBRT-related toxicity. Mortality following surgery at 30 days ranges between 1.1-5.4% and increases up to three-fold to 2.7-9.5% at 90 days (15). Surgical risks are even higher for central tumors as these necessitate complex bronchoplastic and/or angioplastic procedures that may ultimately be converted to pneumonectomy (16,17). For such patients, 30-day mortality is almost 5% and the risk of operative complication approaches 30%. In contrast, when SABR-related mortality occurs, the time to event is approximately 7.5 months (range, 5-12.5 months) (4). Put this into context and consider, that elderly patients who are not offered curative treatment have a median survival of approximately 6 months (2). In an area where literature can be interpreted variably, is continually evolving and often dependent on individual clinician's willingness to administer SBRT, the decision as to whether SBRT should be offered to central NSCLC needs to be patient centered, accounting for individual patient preferences (18). Arguing against using SBRT, risks clinicians assuming 'paternalistic authority' and continues to underestimate the level of involvement patients want in their treatment decisions (19).

Conclusions

The overall quality and extent of literature to guide treatment of central NSCLC with SBRT is limited. Reports against the use of SBRT have significant limitations and appear outweighed by the body of evidence supporting SBRT, which suggest the risk of mortality and morbidity are acceptable with more protracted SBRT courses, in particular 60 Gy in 8 factions. European experts seem to

agree, as this fractionation will be robustly tested in the phase II setting without dose finding (20).

Acknowledgements

None.

Footnote

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

References

1. 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.
2. Haasbeek CJ, Palma D, Visser O, et al. Early-stage lung cancer in elderly patients: a population-based study of changes in treatment patterns and survival in the Netherlands. Ann Oncol 2012;23:2743-7.
3. Vest MT, Herrin J, Soulos PR, et al. Use of new treatment modalities for non-small cell lung cancer care in the Medicare population. Chest 2013;143:429-35.
4. Senthi S, Haasbeek CJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol 2013;106:276-82.
5. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
6. Corradetti MN, Haas AR, Rengan R. Central-airway necrosis after stereotactic body-radiation therapy. N Engl J Med 2012;366:2327-9.
7. Xia T, Li H, Sun Q, et al. Promising clinical outcome of stereotactic body radiation therapy for patients with inoperable Stage I/II non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006;66:117-25.
8. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75:677-82.
9. Bral S, Gevaert T, Linthout N, et al. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: results of a Phase II trial. Int J Radiat Oncol Biol Phys 2011;80:1343-9.
10. Taremi M, Hope A, Dahele M, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. Int J Radiat Oncol Biol Phys 2012;82:967-73.
11. Videtic GM, Reddy CA, Sorenson L. A prospective study of quality of life including fatigue and pulmonary function after stereotactic body radiotherapy for medically inoperable early-stage lung cancer. Support Care Cancer 2013;21:211-8.
12. Daly ME, Perks JR, Chen AM. Patterns-of-care for thoracic stereotactic body radiotherapy among practicing radiation oncologists in the United States. J Thorac Oncol 2013;8:202-7.
13. Mangona VS, Aneese AM, Marina O, et al. Toxicity after central versus peripheral lung stereotactic body radiation therapy: a propensity score matched-pair analysis. Int J Radiat Oncol Biol Phys 2015;91:124-32.
14. Park HS, Harder EM, Mancini BR, et al. Central versus Peripheral Tumor Location: Influence on Survival, Local Control, and Toxicity Following Stereotactic Body Radiotherapy for Primary Non-Small-Cell Lung Cancer. J Thorac Oncol 2015;10:832-7.
15. Senthi S, Senan S. Surgery for early-stage lung cancer: post-operative 30-day versus 90-day mortality and patient-centred care. Eur J Cancer 2014;50:675-7.
16. Chen C, Bao F, Zheng H, et al. Local extension at the hilum region is associated with worse long-term survival in stage I non-small cell lung cancers. Ann Thorac Surg 2012;93:389-96.
17. Spiguel L, Ferguson M. Sleeve lobectomy versus pneumonectomy for lung cancer patients with good pulmonary function. In: Ferguson M, editor. Difficult Decisions in Thoracic Surgery. Springer: London;2007.
18. Barry MJ, Edgman-Levitan S. Shared decision making--pinnacle of patient-centered care. N Engl J Med 2012;366:780-1.
19. Tariman JD, Berry DL, Cochrane B, et al. Preferred and actual participation roles during health care decision making in persons with cancer: a systematic review. Ann Oncol 2010;21:1145-51.
20. debahr S, Collette S, Shash E, et al. LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective. Br J Radiol 2015;88:20150036.

Cite this article as: Woodford K, Senthi S. Pros: should a medically inoperable patient with a T2N0M0 non-small cell lung cancer central in the lung hilus be treated using stereotactic body radiotherapy? Transl Lung Cancer Res 2015;4(5):619-622. doi: 10.3978/j.issn.2218-6751.2015.08.08

Controversy and Debate

Cons: should a medically inoperable patient with a T2N0M0 non-small cell lung cancer central in the lung hilus be treated using stereotactic body radiotherapy?

Ursula Nestle[1,2], José Belderbos[3]

[1]Department of Radiation Oncology, University Medical Center Freiburg, Freiburg, Germany; [2]German Cancer Consortium (DKTK), Heidelberg (partner site Freiburg), Germany; [3]Department of Radiation Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Correspondence to: Prof./Dr. med. Ursula Nestle. Department of Radiation Oncology, University Medical Center Freiburg, Robert-Koch-Str. 3, D-79106 Freiburg, Germany. Email: ursula.nestle@uniklinik-freiburg.de.

Submitted Jun 08, 2015. Accepted for publication Aug 11, 2015.
doi: 10.3978/j.issn.2218-6751.2015.08.07
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2015.08.07

Treating medically inoperable patients with T2N0 NSCLC central in the lung hilus by stereotactic body radiotherapy (SBRT) is a promising treatment option. Unfortunately, solid dose and volume related toxicity data are presently lacking, so that risk estimation for severe toxicities is difficult, while we simultaneously do not have evidence that such treatment would be more effective compared to conventional fractionated radiotherapy.

Why should we be concerned? Beyond the high rate of local control, the success of SBRT for peripheral lung tumors is related to a very low toxicity, as small volumes of fibrosis peripheral in the lung (a parallel structured organ) do mostly not lead to clinically relevant consequences. However, in or near the mediastinum, we are confronted with several serial organs (bronchi, large vessels, esophagus), whose small volume damage may result in clinically severe or even fatal toxicities (1). Evidence for this is found in series with conventionally fractionated radiotherapy or endobronchial brachytherapy. Although we are not completely sure that for high dose per fraction the LQ or LQL model is predictive after SBRT, such data may help to roughly assess the risk (2,3).

For conventionally fractionated radiotherapy, toxicity has been widely studied resulting in reliable models for e.g., radiation pneumonitis as a function of the mean lung dose (MLD) and the lung volume receiving more than a threshold dose (Vx). Borst *et al*. concluded that for high dose per fraction (up to 12 Gy per fraction), the linear quadratic LQ model with an α/β ratio of 3 Gy is the best method for converting the physical lung dose to predict radiation pneumonitis (4). In the context of central tumors, a recent dose escalation study published by Cannon *et al*. (5) with isotoxic planning of a 25 fraction radiotherapy regime, the prescribed dose being related to the risk of pneumonitis. A 5% rate of grade 4 and 5 complications was reported, when an EQD2 of 83 Gy (Dmax) to the central bronchial tree was exceeded. Interestingly, this dose equates to a BED10 of 100 Gy, just what would be necessary to locally control tumors by SBRT. These data do well illustrate the tightrope walk, which we face here: needing a tumor-BED sharply at the risk border to severe toxicities, there is not much room for dose inhomogeneities affecting neighboring serial normal tissues.

In general, patients with central tumors have an increased risk of dying due to a fatal pulmonary hemorrhage. Langendijk *et al*. retrospectively analyzed a large cohort of patients treated for lung cancer to investigate whether endobronchial brachytherapy was a risk factor for fatal bleedings. He analyzed if patients were potential candidates for endobronchial brachytherapy and he selected in this way patients with central tumors. An average fatal bleeding risk of 10.8% in 938 patients, treated with RT and/or brachytherapy was reported (6). The majority of patients were treated with radical conventional RT alone (EQD2, 61.6-72 Gy). Almost half of the 840 patients had bronchoscopy-proven endobronchial tumor in the proximal airways. In this group, the incidence of a fatal bleeding was 13.1%. The multivariate analyses highlighted the presence

of endobronchial tumor (central location) as a significant risk factor, as well as the fraction size of brachytherapy. When a single dose of 15 Gy brachytherapy was used, 47.8% died from massive haemoptysis. Since the large blood vessels are in close vicinity to the bronchi a high dose per fraction (single fraction of 15 Gy) had disastrous results. Beyond normal tissue damage, this may be related to simultaneous tumor invasion of both the bronchus and the vessel: in such a situation, fast tumor shrinkage without the chance for normal tissue re-organization will almost inadvertently be fatal.

The classic principle of radiation treatment is, that normal tissue tolerances are defined by an interaction of total dose, dose per fraction, overall treatment time, type of radiation and the volume treated: serial organ structure versus parallel organ structure. Although the lungs are parallel organs, bronchi and vessels are not, meaning that damage centrally will have a huge impact on the functioning of the ipsilateral lung as a whole. This might be catastrophic especially for medically inoperable patients if the lung tissue peripheral from the damage is eliminated.

Scheenstra *et al*. (7) modeled the relation between local dose and perfusion reduction in lung cancer patients with peripheral lung tumors (>2 cm distance from bronchial tree) treated with SABR. This relation showed a plateau for doses >100 Gy. The relative perfusion reduction was continuously increasing from 4 months up to 15 months after SABR caused by further development of late damage. Reperfusion was not observed. Especially in medically inoperable patients the local perfusion reduction correlates with lung ventilation and is considered to be a surrogate for pulmonary function decline.

We need to speculate whether the perfusion loss seen for peripheral tumors after SABR is also applicable to centrally located tumors. After conventionally fractionated RT we previously reported on reperfusion due to tumor shrinkage of larger and more centrally located tumors (8). So, by conventionally fractionated radiotherapy we might improve the perfusion and pulmonary function, if we treat a patient with a T2N0M0 non-small cell lung cancer located centrally in the lung hilus that compresses a large blood vessel.

In the light of all this evidence, the toxicity rates reported for SABR of central tumors appear surprisingly low. However, as can be seen in the comprehensive review by Senthi *et al*. (9), most of these data come from retrospective mono-center series or case reports. Still, fatal toxicities have been reported with deaths from fatal bleeding, esophageal ulceration and bronchial stenosis/necrosis with subsequent fatal pneumonia (3,10-17). However, due to the mainly retrospective character of the reports, the numbers of cases at risk for certain toxicity are not available. Therefore dose effect relations for toxicity models on hypo-fractionated schedules of centrally located tumors cannot be derived from these data.

Almost all data on SBRT is on medically inoperable patients. A medically inoperable patient is generally of high biological age and fragile, with reduced lung function before treatment because of COPD, intra-thoracic tumor or because they are heavy smokers. Due to the comorbidities causing inoperability, deaths e.g., caused by pulmonary reasons will not automatically be attributed to SBRT toxicity and even sudden deaths will rather be interpreted as consequences of heart disease.

With the paucity of prospective data, the low reported rates of severe toxicities from the SBRT series might also be the result of thorough patient selection in experienced centers.

The situation of a "central tumor in the lung hilus" may imply or not imply an overlap of the PTV with the central airways. The majority of patients reported with "central" SBRT may have target volumes not involving the central bronchial tree, as at least in some of the available publications, the term "central" is rather related to the neighborhood of any part of the mediastinum. Experienced centers and current clinical trial protocols apply tight dose constraints to the central airways and exclude cases with "very central tumors" (18).

Considering the potential indication for a new treatment, a high risk for toxicity would only be justified by a clearly higher effectiveness of new versus conventional treatment or by other factors leading to a clear benefit for the patient. With convincing local control data on SBRT in peripheral tumors, clinical practice has been rapidly changed in favor of short treatment time and patient's convenience. However, to date there is only one prospective randomized trial investigating SBRT *vs*. conventional fractionation, which showed no advantage of SBRT in terms of local control and survival (19). Retrospective data from a German database furthermore showed that SBRT in central tumors if performed with reduced dose—as a potential result from toxicity concerns—may result in worse outcome as compared to peripheral SBRT (20).

Obviously, the advantages of short overall treatment time and patients convenience do also apply for SBRT in central tumors. In order to provide well established standards for

safe application of this treatment, we urgently need larger databases with prospective multicenter data, where we can relate local doses and volumes to well documented toxicities. Therefore, the conduction of quality assured prospective trials with fixed inclusion criteria and thorough follow up are obligatory. The aim to evaluate the use of SBRT also for operable patients in the future furthermore stresses the need for such evidence. It is the task of us as radiation oncology community to do systematic and thorough investigations about the chances and risks of SBRT in central tumors in prospective trials. Based on validly standardized methods, the discussion with the opponents of SBRT will be much easier than on the base of retrospective data.

Overall, we think that SBRT for a medically inoperable case with a T2N0M0 NSCLC in the hilum might be an attractive option in the near future. However, in order to characterize effectiveness and toxicity profiles for future patients in a standardized setting and to elaborate clear procedures for patient selection, planning and conduction of this treatment, more prospective data must be collected before it can be recommended to the general radiation oncology community.

Acknowledgements

None.

Footnote

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

References

1. Nestle U, Faivre-Finn C, DeRuysscher D, et al. Stereotactic body radiotherapy (SBRT) in central non-small cell lung cancer (NSCLC): solid evidence or "no-go"? Radiother Oncol 2013;109:178-9.
2. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? Int J Radiat Oncol Biol Phys 2014;88:254-62.
3. Adebahr S, Collette S, Shash E, et al. LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective. Br J Radiol 2015;88:20150036.
4. Borst GR, Sonke JJ, Belderbos JS, et al. Normal Tissue Complication Probability after hypofractionation increased due to the high dose per fraction or the high total Biological Equivalent Dose? Radiother Oncol 2010;94:388.
5. Cannon DM, Mehta MP, Adkison JB, et al. Dose-limiting toxicity after hypofractionated dose-escalated radiotherapy in non-small-cell lung cancer. J Clin Oncol 2013;31:4343-8.
6. Langendijk JA, Tjwa MK, de Jong JM, et al. Massive haemoptysis after radiotherapy in inoperable non-small cell lung carcinoma: is endobronchial brachytherapy really a risk factor? Radiother Oncol 1998;49:175-83.
7. Scheenstra AE, Rossi MM, Belderbos JS, et al. Local dose-effect relations for lung perfusion post stereotactic body radiotherapy. Radiother Oncol 2013;107:398-402.
8. Seppenwoolde Y, Muller SH, Theuws JC, et al. Radiation dose-effect relations and local recovery in perfusion for patients with non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2000;47:681-90.
9. Senthi S, Haasbeek CJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review. Radiother Oncol 2013;106:276-82.
10. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
11. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75:677-82.
12. Modh A, Rimner A, Williams E, et al. Local control and toxicity in a large cohort of central lung tumors treated with stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2014;90:1168-76.
13. Oshiro Y, Aruga T, Tsuboi K, et al. Stereotactic body radiotherapy for lung tumors at the pulmonary hilum. Strahlenther Onkol 2010;186:274-9.
14. Corradetti MN, Haas AR, Rengan R. Central-airway necrosis after stereotactic body-radiation therapy. N Engl J Med 2012;366:2327-9.
15. Li Q, Swanick CW, Allen PK, et al. Stereotactic ablative radiotherapy (SABR) using 70 Gy in 10 fractions for non-small cell lung cancer: exploration of clinical indications. Radiother Oncol 2014;112:256-61.
16. Nishimura S, Takeda A, Sanuki N, et al. Toxicities of organs at risk in the mediastinal and hilar regions following stereotactic body radiotherapy for centrally located lung tumors. J Thorac Oncol 2014;9:1370-6.

17. Song SY, Choi W, Shin SS, et al. Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. Lung Cancer 2009;66:89-93.
18. Haasbeek CJ, Lagerwaard FJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. J Thorac Oncol 2011;6:2036-43.
19. Nyman J, Hallqvist A, Lund JA, et al. SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. Radiother Oncol 2014;ESTRO 33. Available online: http://cmoffice.estronet.eu/CM.NET.WebUI/CM.NET.WebUI.scpr/SCPRfunctiondetail.aspx?confID=05000000-0000-0000-0000-000000000116&sesID=05000000-0000-0000-0000-000000002447&absID=07000000-0000-0000-0000-000000012544
20. Schanne DH, Nestle U, Allgäuer M, et al. Stereotactic body radiotherapy for centrally located stage I NSCLC: a multicenter analysis. Strahlenther Onkol 2015;191:125-32.

Cite this article as: Nestle U, Belderbos J. Cons: should a medically inoperable patient with a T2N0M0 non-small cell lung cancer central in the lung hilus be treated using stereotactic body radiotherapy? Transl Lung Cancer Res 2015;4(5):623-626. doi: 10.3978/j.issn.2218-6751.2015.08.07

Controversy and Debate

Rebuttal from Ms Woodford and Dr Senthi

Katrina Woodford, Sashendra Senthi

William Buckland Radiotherapy Centre, The Alfred, Melbourne, Victoria, Australia

Correspondence to: Katrina Woodford. William Buckland Radiotherapy Centre, The Alfred, 55 Commercial Rd, Melbourne, Victoria, Australia. Email: katrina.woodford@wbrc.org.au.

Submitted Jun 08, 2015. Accepted for publication Aug 11, 2015.
doi: 10.3978/j.issn.2218-6751.2015.08.11
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2015.08.11

Professor Nestle and Dr. Belderbos' argument against the use of stereotactic body radiotherapy (SBRT) for central non-small cell lung cancer (NSCLC) centers on the fact there is little prospective high quality evidence to declare it safe. This is indeed true and highlights the importance of their multi-national phase II study (LungTech) and RTOG 0813 in guiding optimal patient care (1). However, there are aspects of their argument that should be discussed further, in particular data referenced from Cannon and Langendijk which may not be applicable to T2N0 central NSCLC.

The dose escalation study from Cannon *et al*. assessed patients with locally advanced NSCLC, the vast majority of whom had stage III disease (2). SBRT for such disease represents a significantly higher risk scenario and cannot be used to infer the risks of treating central T2N0 disease. Using a schedule of 50 Gy in ten fractions (BED_3 =133 Gy), Milano *et al*. observed a 40% (4/10) crude risk of treatment related death for node-positive stage II-III NSCLC following SBRT (3). Despite almost doubling the biologic equivalent dose, Chaudhuri *et al*. found an SBRT scheme of 50 Gy in five fractions (BED_3 =217 Gy) for node negative tumors directly abutting the major airways (including the trachea), resulted in no grade 2 or higher toxicity at 2 years (4). Even with small patient numbers it is clear there is a distinction between these clinical scenarios.

The endobronchial brachytherapy study from Langendijk *et al*. indeed found that almost half the patients receiving a single 15 Gy fraction died of massive hemoptysis (5). However, as stated in the paper, using a brachytherapy prescription of 15 Gy at 1 cm, results in catheter and potentially bronchial surface doses of 90-105 Gy. Here the principle organ at risk receives a significantly higher dose than the tumor itself and such toxicity is not surprising. Exactly the opposite is true with SBRT, whereby modern delivery techniques result in planned doses to the adjacent bronchus being significantly less than the center of the tumor.

Professors Nestle and Belderbos also postulate that conventional radiotherapy for large and/or central tumors has the potential to improve lung reperfusion, while SBRT will almost certainly reduce it and consequently decrease pulmonary function. Although we have witnessed extreme examples of this (6), generally following SBRT patients do not appear to suffer any quality of life detriment (7). In a prospective study of patient reported quality of life, central location did not influence global health status and respiratory symptoms, respectively measured by standardized EORTC questionnaires QLQ C30 and QLQ LC13 (8).

Clearly SBRT for central tumors has complexities beyond those for peripheral tumors and should not represent the starting point for a new SBRT program. The need for more high quality data has rightly compelled some within the radiation oncology community to place considerable effort into seeking it. Until then, the available data appears to be sufficient for clinicians to offer willing patients the opportunity for cure when SBRT is their only or preferred treatment option.

Acknowledgements

None.

Footnote

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

References

1. Adebahr S, Collette S, Shash E, et al. LungTech, an EORTC Phase II trial of stereotactic body radiotherapy

for centrally located lung tumours: a clinical perspective. Br J Radiol 2015;88:20150036.
2. Cannon DM, Mehta MP, Adkison JB, et al. Dose-limiting toxicity after hypofractionated dose-escalated radiotherapy in non-small-cell lung cancer. J Clin Oncol 2013;31:4343-8.
3. Milano MT, Chen Y, Katz AW, et al. Central thoracic lesions treated with hypofractionated stereotactic body radiotherapy. Radiother Oncol 2009;91:301-6.
4. Chaudhuri AA, Tang C, Binkley MS, et al. Stereotactic ablative radiotherapy (SABR) for treatment of central and ultra-central lung tumors. Lung Cancer 2015;89:50-6.
5. Langendijk JA, Tjwa MK, de Jong JM, et al. Massive haemoptysis after radiotherapy in inoperable non-small cell lung carcinoma: is endobronchial brachytherapy really a risk factor? Radiother Oncol 1998;49:175-83.
6. Senthi S, Ullmann EF, Senan S. Pulmonary atelectasis after stereotactic ablative radiotherapy for a central lung tumor. J Thorac Oncol 2013;8:e94-5.
7. Lagerwaard FJ, Aaronson NK, Gundy CM, et al. Patient-reported quality of life after stereotactic ablative radiotherapy for early-stage lung cancer. J Thorac Oncol 2012;7:1148-54.
8. van der Voort van Zyp NC, Prévost JB, van der Holt B, et al. Quality of life after stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2010;77:31-7.

Cite this article as: Woodford K, Senthi S. Rebuttal from Ms Woodford and Dr Senthi. Transl Lung Cancer Res 2015;4(5):627-628. doi: 10.3978/j.issn.2218-6751.2015.08.11

Controversy and Debate

Rebuttal from Dr Nestle and Dr Belderbos

Ursula Nestle[1,2], José Belderbos[3]

[1]Department of Radiation Oncology, University Medical Center Freiburg, Freiburg, Germany; [2]German Cancer Consortium (DKTK), Heidelberg (partner site Freiburg), Germany; [3]Department of Radiation Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Correspondence to: Prof./Dr. med. Ursula Nestle. Department of Radiation Oncology, University Medical Center Freiburg, Robert-Koch-Str. 3, D-79106 Freiburg, Germany. Email: ursula.nestle@uniklinik-freiburg.de.

Submitted Aug 07, 2015. Accepted for publication Aug 11, 2015.
doi: 10.3978/j.issn.2218-6751.2015.08.06
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2015.08.06

We fully agree that in a case when a patient with a T2N0M0 NSCLC central in the hilum has no other curative treatment option and is not eligible for conventionally fractionated radiotherapy, we can discuss with him/her the potential risk of SBRT and the weakness of the available data and may offer this treatment when the patient agrees to bear this risk.

However, this discussion should clearly be aware of the fact that most populations published so far are retrospective and therefore highly selected concerning the location of the tumor and that the idea that the risk is somewhere in the order of magnitude of resection may just be a consequence from this selection. Furthermore it should be kept in mind, that the toxicity in cases of "ultra-central" tumors might be much higher with hypofractionated regimens as compared to conventional fractionation.

When we focus our literature reviews to central tumors treated with high SBRT doses, we neglect the fact that due to toxicity concerns, patients treated outside of clinical trials may receive "SBRT" with insufficient dose. These patients will likely have worse tumor control, as it was seen in the German database analysis (1).

To safely define the therapeutic bandwidth between tumor control and normal tissue toxicity for patients with central tumors profound prospective data are urgently needed. Furthermore, if we aim to further establish SBRT in the future as an alternative to resection also for central and "ultra-central" tumors, we will have problems without prospectively collected outcome and toxicity data. These data can only be obtained by prospective trials or at least from prospective databases including standardized follow up performed by the treating radiation oncologist.

Cite this article as: Nestle U, Belderbos J. Rebuttal from Dr Nestle and Dr Belderbos. Transl Lung Cancer Res 2015;4(5):629. doi: 10.3978/j.issn.2218-6751.2015.08.06

Acknowledgements

None.

Footnote

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

References

1. Schanne DH, Nestle U, Allgäuer M, et al. Stereotactic body radiotherapy for centrally located stage I NSCLC: a multicenter analysis. Strahlenther Onkol 2015;191:125-32.

Future Direction

Surgery or stereotactic ablative radiation therapy: how will be treated operable patients with early stage not small cell lung cancer in the next future?

Luca Bertolaccini[1], Alberto Terzi[1], Francesco Ricchetti[2], Filippo Alongi[2]

[1]Thoracic Surgery Unit, [2]Radiation Oncology Department, Sacro Cuore-Don Calabria Hospital, 37024 Negrar Verona, Italy

Correspondence to: Luca Bertolaccini, MD, PhD, FCCP. Thoracic Surgery Unit, Sacro Cuore-Don Calabria Hospital, Via Don Angelo Sempreboni 5, 37024 Negrar Verona, Italy. Email: luca.bertolaccini@gmail.com.

Abstract: Lung neoplasm is the most influent cause of death for cancer. With the increasing of life expectancy in elderly patients and with the intensification of lung cancer screening by low-dose computed tomography, a further rise of the number of new non-small cell lung cancer (NSCLC) cases has been shown. Standard of care of early stage NSCLC patients is lobectomy but approximately 20% of them are not fit for surgery for comorbidities. Due to the high local control rates and the little adverse effects, stereotactic body radiation therapy (SBRT) also called stereotactic ablative radiation therapy (SABR), has rapidly replaced the conventional radiotherapy in not operable patients with stage I NSCLC. We review the evidence for use of SABR in medically inoperable patients with stage I NSCLC, and its possible extension of use to operable patients, from the perspectives of radiation oncologists and thoracic surgeons. Until the results of large randomized trials will be available, the multidisciplinary management, balancing during discussion the advantages/disadvantages of each treatment modality, could be the coming soon best approach for medically operable early-stage NSCLC. As a result, the minimally invasive thoracic surgery advantages and the SABR innovations will be translated into real clinical benefits.

Keywords: Early stage non-small cell lung cancer (NSCLC); video-assisted thoracic surgery (VATS); stereotactic ablative radiation therapy (SABR)

Submitted Dec 04, 2014. Accepted for publication Dec 04, 2014.
doi: 10.3978/j.issn.2305-5839.2015.01.06
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.01.06

Primary malignant lung disease represents the most influent cause of death for cancer in US. With the increasing of life expectancy in elderly patients and with the intensification of lung cancer screening by low-dose computed tomography, a further rise of the number of new non-small cell lung cancer (NSCLC) cases has been shown as continuous and consistent (1,2). Stereotactic body radiation therapy (SBRT), also called stereotactic ablative radiation therapy (SABR) has been developed as an innovative therapy for stage I NSCLC and has now emerged as a standard treatment option for medically inoperable patients. We review the evidence of SABR in medically inoperable patients with stage I NSCLC, and the possible extension to operable patients, from the perspectives of radiation oncologists and thoracic surgeons.

Pro stereotactic ablative radiation therapy (SABR)

Standard of care of early stage NSCLC patients is lobar resections but approximately 20% of them are not suitable for surgery resection for severe cardiac and/or respiratory comorbidities. If untreated, the 5 years mortality lung cancer related is dramatically high, around 90% (3). Radiation therapy has been traditionally indicated in these cases. Using conventional external beam radiation doses, survival has been influenced only with an extension of 7 months in median survival compared to patients submitted only to observation (2,3). In fact, doses of 60-70 Gy, prescribed in conventional fractionated 3D-conformal radiotherapy, lead to

disappointing local control rates of only 30-50% for stage I disease and therefore could not meet the demand to replace surgery.

SBRT was born in the 1990s, as an extracranial application of the well-known radiosurgery approach that uses spatial coordinates to define the position to irradiate target with massive radiation doses. Today, the concept is rapidly changing and with the term SBRT, we identify a "philosophy" for treating cancer in the body not necessarily with spatial coordinates, but essentially prescribing high focused doses in one or few sessions. Over the last few decades, more sophisticated stereotactic, intensity-modulated (IMRT) and image-guided techniques (IGRT) of delivering radiation have allowed clinicians to safely prescribe higher doses than in the past, frequently with hypofractionated schedules (high dose per fraction in few fractions) (4) in several settings. "Dose sculpting" on lung tumor with IMRT is a helpful approach to minimize the radiation dose to healthy surrounding tissues. IGRT reduces repositioning errors and is used to monitor the treatment region and/or to adapt dose distribution to the possibly changing target and organs at risk during radiation (5). Nowadays, four-dimensional CT (4DCT) for planning, active breath control during delivery, tracking the lesion and delivery the dose following respiratory motion, are some of the more common strategies to manage the uncertainties of the movement of the target, especially in the thorax. Recent clinical data has shown that SBRT for peripheral lesions of inoperable patients with early stage NSCLC is able to achieve outcomes comparable to that of surgery (6,7). For early stages of NSCLC, using biological effective doses (BED) greater than 100 Gy, 5-year controls are approximately 85-90% (6,7).

Thus, in the range of 8-20 Gy per fraction, SBRT effect becomes disruptive and it has been defined as SABR. Prevalent phenomena such as endothelium apoptosis and stoma damage has been involved to justify the impressive improvement in local control when ablative doses were prescribed (8,9). According to several international guidelines, SABR is now recommended as the standard curative treatment for medically inoperable patients with early stage NSCLC (10-12). The impact of introducing SABR in the therapeutic scenario was estimated: a significant cost savings and survival gains was found for stage I NSCLC in Canadian patients (13). While SABR is a well defined curative treatment option in medically inoperable patients, its role in the patient suitable for curative surgery is yet to be defined. To date, the large amount of data of SABR for early stage NSCLC regards populations of patients excluded from surgery. Although the local control rates in these patients have been optimal, 3-year overall survival rates remain limited in several series, between 43% and 60%, probably due to deaths related to intercurrent illness (14,15). The absence of randomized trials in this setting does not imply the absence of potential evidence on efficacy of SABR as well as surgery in early stage operable NSCLC patients. A meta-analysis was performed by Zheng *et al.* (16) including forty SABR studies (4,850 patients) and 23 surgery studies (7,071 patients), published in the same period. Population profiles differed between SABR and surgery patients about comorbidities and age. Better treatment outcomes were provided by surgery. Nevertheless, adjusting patient profile differences, extrapolative analysis shows that SABR produced non-inferior survival outcomes in comparison to surgery, especially in patients with operable stage I NSCLC. When SABR is compared with surgery, a consideration concerning the type of resection seems to be also crucial. Recently, 9,093 early-stage, node-negative NSCLC patients who underwent definitive treatment including lobectomy, sublobar resection, and SABR were evaluated for a propensity score-matching well-matched analysis. Compared to lobectomy, sublobar resection was associated with worse overall survival rate; SABR and lobectomy cohorts' demonstrated similar overall survival in both groups. Being sublobar resection suboptimal when compared to lobar surgery, and being SBRT equivalent to the last one, it could be indirectly assumed that SABR is superior to sublobar resection (17). It was confirmed by Port in a propensity-matched analysis of wedge resection and SABR proposed to 164 early stage NSCLC patients poor candidates for lobar resection. In patients treated by SABR, higher overall, disease recurrence rate was shown compared to those treated by wedge Resection. Nevertheless, no difference between the two groups in disease-free 3-year survival was found (18). Several criticisms remain about a comparison between surgery and SABR because of the different definitions of local recurrence, and heterogeneity in the type of SABR across different centers (19). However, where data are available, the impact of SABR in operable setting is certainly not negligible. In a Japan Group study, nearly 100 stage I patients who refused surgery were evaluated: the 5-year overall survival rate achieved prescribing a BED of at least 100 Gy was 70.8% (20). Starting to these backgrounds, two randomized phase III trials (21) have been initiated to randomize stage I NSCLC medically

operable patients to receive SBRT or the gold standard of surgical resection. The results of these trials could modify radically the treatment strategy for these patients. A report regarding operable NSCLC patient's interviews clearly shown how patients averse to taking risks involving the possibility of immediate death (22). Undoubtedly, if the SBRT and surgical resection result as similarly effective, patients may be hesitant to be submitted to a treatment procedure that involves an upfront mortality risk. Thus, the decision between SABR and surgery will be defined patient per patient, based on the relative merits and pitfalls of each treatment approach. The results of SABR are promising and other data in this direction will certainly arrive from ongoing studies. However, follow-up of lobectomy series are longer and these solid data should not be ignored. Conversely, the relative high surgical mortality rate could be crucial in decision-making strategy for patients who are averse to have any kind of risk of operative-related death. Multidisciplinary management, balancing during discussion the advantages/disadvantages of each treatment modality, could be the coming soon best approach for medically operable early-stage NSCLC (23).

Pro surgery

Due to the high local control rates and the little adverse effects, SABR has rapidly replaced the conventional radiotherapy in not operable patients with stage I NSCLC (24). A few well-designed prospective studies have proven that SABR is safe and effective for medically inoperable NSCLC patients (13). After that, some authors reported a short/medium term local control comparable to surgery in series of NSCLC patients who refused surgery, and others reported no differences in overall survival, disease-specific survival, and local control (20,25). Senan *et al*. further reported that SABR achieves similar control rates of surgery without the risks associated to surgery (26). Due to these provocative results, a few authors evidenced that these studies were retrospective and uncontrolled, and subject to some biases (19,27). First, the local control rate favorable for SABR is only referred to the primary tumor site. Second, the residual parenchymal scar after SABR is difficult to differentiate from cancer (17). On the contrary, the local failure rate of surgical series included not only recurrences within the same lobe away from the primary site, but also recurrence in ipsilateral lung (16); therefore, the controversial finding could be a result of differences in the definition of local tumor control (17). Actually, only a few studies (24-27) compare the clinical outcomes of surgery and SABR in early stage NSCLC, using a case-matched analysis, while others were based on non-randomized data or observational series (28). Another unresolved issue of SABR is the lack of pathological confirmation of the tumor and the resected lymph nodes that are mandatory to correctly stage the disease and to pose the indication of adjuvant chemotherapy. Therefore, to compare either retrospective or prospective series, only patients with biopsy-proven cancers should be included. Furthermore, these issues have to be investigated through long-term follow-up of previous clinical trials (29). Randomized phase III trials or large population cohort studies have not been completed; several randomized trials were initiated but they were stopped due to poor accrual (30). Lastly, regarding the little adverse effects from SABR for early stage NSCLC, various serious complications have been reported in numerous studies (31).

Nowadays, thoracic surgery remains the treatment of choice for the early stage NSCLC patients. The wider and wider adoption of the video-assisted thoracic surgery (VATS) techniques has reduced the postoperative morbidity and has led to a decreased hospital length of stay. The increased ability to identify small NSCLC by low dose computed tomography-screening programs arose the question whether or not lobectomy is appropriate in this subset of patients with small size early stage NSCLC (32). Sublobar resections have demonstrated the safety of their perioperative course, the effectiveness of preservation of pulmonary function (in comparison with lobectomy), and the comparable oncologic outcomes (32). To date, sublobar resection is performed most often as an alternative to lobectomy in patients with peripheral tumors with limited pulmonary reserve or other comorbidities (32,33). The medical community is still searching a spirometric cut-off value that could suggest the indication to SABR approach instead of surgery. The thresholds for radical treatment of patients with lung cancer are rapidly changing; therefore, the exclusively use of FEV1 and DLCO may no longer be sufficient and the current guidelines suggest standardized protocols for risk assessment (34).

Conclusions

Until the results of large randomized trials will be available, the multidisciplinary management, balancing during discussion the advantages/disadvantages of each treatment modality, could be the coming soon best approach for

medically operable early-stage NSCLC. Multidisciplinary teams should include experienced thoracic surgeons, radiation oncologists, and medical oncologists. As a result, the VATS advantages and the SABR innovations will be translated into real clinical benefits.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
2. Raz DJ, Zell JA, Ou SH, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. Chest 2007;132:193-9.
3. Wisnivesky JP, Bonomi M, Henschke C, et al. Radiation therapy for the treatment of unresected stage I-II non-small cell lung cancer. Chest 2005;128:1461-7.
4. Blomgren H, Lax I, Näslund I, et al. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 1995;34:861-70.
5. Alongi F, Di Muzio N. Image-guided radiation therapy: a new era for the radiation oncologist? Int J Clin Oncol 2009;14:568-9.
6. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352-8.
7. Nagata Y, Wulf J, Lax I, et al. Stereotactic radiotherapy of primary lung cancer and other targets: results of consultant meeting of the International Atomic Energy Agency. Int J Radiat Oncol Biol Phys 2011;79:660-9.
8. Garcia-Barros M, Paris F, Cordon-Cardo C, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science 2003;300:1155-9.
9. Alongi F, Di Muzio N. Radiobiology and molecular oncology: how are they changing radiotherapy in clinical practice? Tumori 2010;96:175-7.
10. NCCN clinical practice guidelines in oncology: Non-small cell lung cancer. Version 2. 2014. Available online: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
11. Potters L, Kavanagh B, Galvin JM, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2010;76:326-32.
12. Crinò L, Weder W, van Meerbeeck J, et al. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21:v103-15.
13. Louie AV, Rodrigues G, Hannouf M, et al. Stereotactic body radiotherapy versus surgery for medically operable Stage I non-small-cell lung cancer: a Markov model-based decision analysis. Int J Radiat Oncol Biol Phys 2011;81:964-73.
14. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.
15. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75:677-82.
16. Zheng X, Schipper M, Kidwell K, et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis. Int J Radiat Oncol Biol Phys 2014;90:603-11.
17. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. JAMA Surg 2014;149:1244-53.
18. Port JL, Parashar B, Osakwe N, et al. A propensity-matched analysis of wedge resection and stereotactic body radiotherapy for early stage lung cancer. Ann Thorac Surg 2014;98:1152-9.
19. Van Schil PE, Van Meerbeeck J. Surgery or radiotherapy for early-stage lung cancer--a potential comparison bias. Lancet Oncol 2013;14:e390.
20. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100.
21. Hurkmans CW, Cuijpers JP, Lagerwaard FJ, et al. Recommendations for implementing stereotactic radiotherapy in peripheral stage IA non-small cell lung cancer: report from the Quality Assurance Working Party of the randomised phase III ROSEL study. Radiat Oncol 2009;4:1.
22. McNeil BJ, Weichselbaum R, Pauker SG. Fallacy of the five-year survival in lung cancer. N Engl J Med

1978;299:1397-401.
23. Louie AV, Senthi S, Palma DA. Surgery versus SABR for NSCLC. Lancet Oncol 2013;14:e491.
24. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:348-53.
25. Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2010;140:377-86.
26. Senan S, Paul MA, Lagerwaard FJ. Treatment of early-stage lung cancer detected by screening: surgery or stereotactic ablative radiotherapy? Lancet Oncol 2013;14:e270-4.
27. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol 2010;28:928-35.
28. Parashar B, Patel P, Monni S, et al. Limited resection followed by intraoperative seed implantation is comparable to stereotactic body radiotherapy for solitary lung cancer. Cancer 2010;116:5047-53.
29. Onishi H, Araki T. Stereotactic body radiation therapy for stage I non-small-cell lung cancer: a historical overview of clinical studies. Jpn J Clin Oncol 2013;43:345-50.
30. Timmerman RD, Fernando HC. A radiation oncologist's and thoracic surgeon's view on the role of stereotactic ablative radiotherapy for operable lung cancer. Semin Thorac Cardiovasc Surg 2013;25:8-13.
31. Lo SS, Sahgal A, Chang EL, et al. Serious complications associated with stereotactic ablative radiotherapy and strategies to mitigate the risk. Clin Oncol (R Coll Radiol) 2013;25:378-87.
32. Altorki NK, Yip R, Hanaoka T, et al. Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. J Thorac Cardiovasc Surg 2014;147:754-62; discussion 762-4.
33. De Ruysscher D, Nakagawa K, Asamura H. Surgical and nonsurgical approaches to small-size nonsmall cell lung cancer. Eur Respir J 2014;44:483-94.
34. Brunelli A, Charloux A, Bolliger CT, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J 2009;34:17-41.

Cite this article as: Bertolaccini L, Terzi A, Ricchetti F, Alongi F. Surgery or stereotactic ablative radiation therapy: how will be treated operable patients with early stage not small cell lung cancer in the next future? Ann Transl Med 2015;3(2):25. doi: 10.3978/j.issn.2305-5839.2015.01.06

Future Direction

Stereotactic body radiation therapy (SBRT) for non-small cell lung cancer (NSCLC): current concepts and future directions

Steven W. Davis, Douglas A. Rahn III, Ajay P. Sandhu

Department of Radiation Medicine and Applied Sciences, San Diego School of Medicine, University of California, San Diego, USA
Correspondence to: Ajay Sandhu, MD. Department of Radiation Oncology, University of California, San Diego, Moores UCSD Cancer Center, 3960 Health Sciences Drive #0865, La Jolla, CA 92093-0865, USA. Email: apsandhu@ucsd.edu.

Abstract: The standard of care for treatment of early-stage lung cancer continues to be definitive surgery with lobectomy or pneumonectomy. However, there are patients who refuse surgery or due to several factors, including high operative risk, are not surgical candidates. Fractionated, standard-dosed radiation has been shown to offer suboptimal control and survival rates. In these patients, stereotactic body radiotherapy (SBRT) is increasingly becoming a viable, safe, and effective alternative to surgery. An emerging and expanding body of evidence is showing the technical feasibility and ablative properties of relatively short courses and high doses of SBRT. This review will focus on the emergence of the technique, the current status of its use and the future directions of study that will further define how we use SBRT in the treatment of early stage non-small cell lung cancer (NSCLC).

Keywords: Stereotactic body radiotherapy (SBRT); lung cancer; non-small cell lung cancer (NSCLC); pathologic diagnosis; radiotherapy

Submitted Jun 18, 2014. Accepted for publication Jul 04, 2014.
doi: 10.3978/j.issn.2218-676X.2014.07.02
View this article at: http://dx.doi.org/10.3978/j.issn.2218-676X.2014.07.02

Introduction

It is estimated that there will be over 226,000 new diagnoses and 159,000 deaths from lung cancer in the United States in 2014 (1). In fact, lung cancer deaths annually total more than deaths from breast, prostate, colon, brain and uterine cancer combined. Additionally, lung cancer is the leading cause of cancer mortality in both men and women worldwide, with estimated incidence rates of over 2 million cases annually, and death rates nearing 1.5 million annually (2,3). One major reason lung cancer continues to be such a major contributor to cancer deaths includes the combination of the late stage of diagnosis of the majority of cases, and the lack of an accepted, widely instituted screening program to detect early stage disease. At present, only about 15% of lung cancers are diagnoses at an early stage (stage I and II) and over half are diagnosed with metastatic disease (1).

Smoking has been well established as a leading risk factor for lung cancer. Despite the recent decreases in smoking rates in the US (4), these reduced rates will likely not result in a near-term decline in lung cancer mortality. With a current base of over 90 million current or former smokers, lung cancer will continue to pose a major challenge for the foreseeable future (5). Worldwide, lung cancer rates are expected to rise in the coming years due to the increased prevalence of smoking in developing countries (5). Other significant risk factors for lung cancer include exposure to radon gases and occupational exposures such as asbestos and arsenic. Recent advances in our understanding of tumor biology have also helped us understand more about predictive and prognostic factors in lung cancer. DNA repair pathways such as ERCC-1 (6) EGFR and ALK mutational status (7), in addition to several other emerging molecular targets will likely play a pivotal role in the prognosis and treatment decisions in lung cancer in the years to come.

Recent efforts to institute a lung cancer screening program have had some success. The lung cancer screening trial, published in 2011, showed that in current or heavy previous smokers between 55-74, conducted prospectively, that there was a 20% reduction in mortality for those screened with low dose helical CT scan *vs*. those with chest X-ray (8). The American Cancer Society and the American

Thoracic Society have issued screening recommendations. Recently, the United States Preventive Task Force has also voiced their support and recommended screening for individuals between 55 and 80 who currently smoke or have a 30 pack year smoking history who have quit within the previous 15 years. Unfortunately, the Task Force also limits its recommendation for screening to those with the willingness or ability to have curative lung surgery. This may exclude patients that may benefit from the other emerging treatment modality for early stage lung cancer, stereotactic body radiotherapy (SBRT). Despite this, there is hope that implementation of screening methods in the coming years may increase the percentage of lung cancer diagnosed in earlier, more treatable stages, and may help further develop SBRT as a reasonable treatment approach.

Treatment of early stage lung cancer

The standard of care for definitive treatment of early stage lung cancer continues to be surgical resection with lobectomy or pneumonectomy. Several large trials have been reported, showing five year overall survival for patients with stage IA and IB disease of 71.25% and 57%, respectively (9-11). Lesser surgical resections, to include wedge resections, have shown worse local control and a trend toward worse overall survival (12). Less invasive techniques continue to be evaluated, but the current standard surgical approach remains thoracotomy (11).

Patients who either decline surgery or are considered unacceptable surgical candidates due to morbidity or mortality concerns are generally offered treatment with radiation therapy alone. Using traditional methods to deliver radiation therapy, results for these patients have been inferior to those for patients treated with surgical resection. There are several potential explanations for these worse outcomes. First, there is an obvious selection bias. Patients treated with radiation represent a high-risk group of patients with more medical comorbidities and resultant worse performance status than those patients offered surgical treatment. Secondly, the patients treated with surgery alone undergo pathological staging as opposed to the clinical-only staging of the patients treated with radiation alone. Undoubtedly some patients with clinically early stage disease would have been found to have more advanced disease on formal pathologic analysis (13). This is especially true for studies before the more modern CT or even PET/CT era. Still, it must be remembered that reported results for patients treated with radiation alone have shown worse local control as well as survival than those seen with resection. Reported 5-year survival in patients treated with traditional radiation treatment range from 6-32%. Local-only failure has been reported in 39-55% of patients (14-17).

The dose of radiation used in treating these patients remained stable for many years. Based on the increased radiologic control seen with increasing dose in RTOG 7301, the standard radiation dose has been 60 Gy. About 65% of the patients treated with at least 60 Gy were found to have local control (18). However, these results likely overstate the true rate of local control with this radiation dose, given their reliance on clinical evidence of local failure. Another series evaluated local control more rigorously (including bronchoscopy) and found local control after 65 Gy given without or with combination chemotherapy of 17% and 15%, respectively (19).

Multiple strategies for improving outcomes with radiation alone have been employed. The most obvious approach has been with dose escalation of conventionally-fractionated radiation. One cooperative group trial reported outcomes with doses of up to 83.8 Gy for patients with V20 of <25% using a fraction size of 2.15 Gy. This phase I/II trial demonstrated acceptable toxicities but did not show a dose response across the range of 70.9-83.8 Gy (20). Unfortunately, a large multi-institutional randomized controlled study comparing 60-74 Gy in locally advanced patients, also failed to show any survival benefit (21). However, other single institution studies have been reported, with a series from Michigan delivering doses as high as >100 Gy with acceptable toxicities (22). A series from Memorial Sloan Kettering Cancer Center (MSKCC) showed a local control advantage with increased dose, with local control at 2 years of 14% for stage I-II patients receiving <80 Gy and 88% for like-stage patients receiving >80 Gy. This series also reported a doubling in medial survival for patients treated with >80 Gy (23).

Another important treatment approach that has been affirmed in the above studies, mostly in an effort to minimize toxicity, has been to avoid elective nodal irradiation (ENI), and instead target only areas of gross disease. The results of these and other series offer strong arguments against the elective treatment of at-risk areas of lymph drainage without evidence of malignant involvement (24). An early report from MSKCC showed a crude rate of elective nodal failure in 171 patients treated without ENI of 6.4% (25); the 2-year actuarial rate of failure was 9%. In RTOG 9311 and the series from Michigan, no ENI was used and the resultant

failure in these areas was less than 10% (20) and zero (22), respectively.

Rationale for stereotactic radiotherapy

Standard fractionated radiation treatment is usually given over a course of 6 to 7 weeks, at 1.8-2.0 Gy per fraction. Changes to this schedule, such as increasing dose with a longer course of conventional fractionation has had mixed success of improving local control. One important consideration in dose escalation involves the increase amount of time required to give larger overall doses. Any advantage gained by an increase in dose must be balanced against a detriment seen with prolongation of overall treatment time. There are radiobiologic studies to support this dilemma. One modeling study suggested that conventionally-fractionated doses of >100 Gy would be required to provide 90% local control at 30 months. To achieve this dose would require 10 weeks, instead of the usual 6-7 weeks, of treatment with conventional fractionation (26).

Another problem is that treatment interruptions are more frequent with increasing radiation dose. Analysis of three RTOG trials from the 1980s showed a detriment in overall survival, particularly seen in patients with otherwise favorable prognostic factors (27). Another pooled-analysis of three RTOG trials from the 1990s evaluated treatment time as a continuous variable. Of 474 total patients analyzed, 18% (n=87) patients had prolongation of treatment time of more than five days. Multivariate analysis showed that each day of prolongation translated to a 2% increase in risk of death (28). Hyperfractionation, or more than one daily fraction spaced at least 6 hours apart, is one approach to try and avoid prolonged treatment delivery times. However, once again, results have thus far have been mixed (29-31).

SBRT, in contrast, allows for a high dose to be delivered in one or only a few treatment fractions. This is possible based off technical advances with the use of intensity modulation using, for example, multi-leaf collimation. There are several potential advantages gained with this treatment method. These include prevention of accelerated repopulation, the ability to treat with BEDs in excess of 100, and treating to a point on the steepest portion of the cell survival curve (26,32,33). There is also the added convenience for the patient of requiring few trips for treatment. Using SBRT techniques to treat malignancy is becoming the object of study in several areas of the body. Tumors of the liver, pancreas, cervix and head and neck have growing bodies of evidence suggesting the role of SBRT in management in certain situations. In the brain, radiosurgery (SRS, single fraction stereotactic radiation therapy) has a well-established role in the treatment of both benign and malignant tumors. Intracranial targets appear particularly well-suited to radiosurgical approaches. Reasons for this include, first, bony anatomy is a reliable surrogate for target position (34) and second, reliable immobilization can help eliminate internal intrafraction target motion (35). Contrarily, thoracic targets are neither well-localized by external anatomy nor are they static (36,37). These represent the two largest treatment-delivery related hurdles to delivering SBRT to targets within the lungs, and several techniques and devices have been developed to overcome these problems.

Motion management

Historically, achievement of reproducible patient positioning and thus accuracy, was best accomplished with the use of a rigid external frame. This is, in fact, the essence of stereotaxy, defined as the use of position and movement through space. True stereotactic treatment relies on the generation and use of an external 3-dimensional (3D) coordinate system; any point within this coordinate system can be positionally described by its relation to the external framework. However, the use of rigid external frames has its own limitations. They tend to be cumbersome, large and often require sedation or other methods of pain control in order to be tolerated by patients. In the last two decades, we have seen the emergence of imaging coupled with the treatment machine with 3D techniques, so called “on board imaging”. One example of this imaging is Cone Beam Computed Tomography (CBCT). Producing a 3D CT scan in real time can achieve comparable localization to stereotaxy. The addition of placement of implanted fiducial markers, discussed in more detail below, may offer an even more robust and reproducible framework for accuracy of tumor targeting.

Intrafraction motion management presents another impediment to lung SBRT. Once again, recent technical advancements are helping overcome this obstacle. Roughly, these technical advancements can be divided into two groups. The first group allows the target to move freely relative to the treatment beams, but accounts for this motion with either geometric or dosimetric considerations. The most basic technique employs the concept of an integrated tumor volume (ITV). Early SBRT studies of

the lung utilized this method. It includes the addition of margins based on population averages. For example, looking at typical inspiratory and expiratory position changes, a plan may involve arbitrarily adding 2 cm in all directions in all cases. In most cases, this population-derived margin is bigger than required and results in treatment of a larger volume of normal lung. The addition of patient-specific margins can be achieved by using fluoroscopic monitoring of target motion throughout the respiratory cycle. An emerging technique, most commonly described as 4D CT scanning, can scan throughout physiologic movement and place position into specified bins of location for each phase of the respiratory cycle. Less technically, one may obtaining both end-inspiratory and end-expiratory imaging and creating a planning target volume that encompasses both extremes.

Strategies in the second group are aimed at maintaining the target position relative to the treatment beams throughout treatment. Within this group are techniques aimed at reducing target motion. Some of these include abdominal compression, deep inspiratory breath hold (DIBH), or forced shallow breathing. Also within this group are techniques which allow for target motion but adjust treatment delivery to maintain constancy between target and treatment beams. These include respiratory gating, beam tracking, or couch-based motion compensation. Data are published that support these techniques. For example, in patients treated for liver metastases, application of abdominal pressure has been found to reduce excursion of the diaphragm to 7 mm (38). DIBH has been shown to increase total lung volume, decrease lung mass within expansion margins, and provide relatively reproducible target displacements (39). Another series found DIBH to be reproducible and reported a potential 30% decrease in the V25 by reducing required target margins (40). Reducing margins from 2.5 to 0.5 cm was shown to decrease by 66% the amount of normal lung in the treatment volume.

Respiratory gating requires use of a modern CT simulation machine able to obtain data in four dimensions, dividing the respiratory cycle into typically 10 bins. This allows target visualization throughout the respiratory cycle and selection of an appropriate range of phases for treatment planning and delivery. At the time of treatment, the patient's respirations are monitored via a reflective box placed on the midsection and the treatment beam is selectively turned off and on at the predetermined phases of respiration (41).

Implanted fiducial markers can be used both for patient positioning as well as target tracking during treatment delivery (42). Using an implanted gold marker seed, one series found that real-time tracking with free breathing could be utilized. In this series, the treatment beam was gated based on the position of the gold marker, successfully reducing the target motion during beam delivery to within 5.3 mm (43).

Beam tracking is another technique. Systems using a dynamic robotic arm and traditional linear accelerators with multi-leaf collimators are both able to track target motion through the sliding collimator leaves (44,45). Finally, there is interest in couch-based motion management, in which the treatment couch motion is equal and opposite to target motion; this technique may be able to maintain consistency in the beam's eye view during treatment delivery (46).

At our institution, we routinely use SBRT for treatment of early stage lung cancer. At the time of simulation, 4D CT scans are obtained to delineate an ITV. Tight margins in the range of 5-7 mm are employed around the ITV to limit dose to normal lung tissue and other critical organs near the target. The use of a gating technique is individualized based on quantitative tumor motion. We use an algorithm that employs respiratory gating in patients with more than 5 mm of motion on 4D CT in those with non-apical tumors. The gating window is determined based on the pattern of tumor motion during different phases of respiratory cycle. A typical plan for SBRT of a primary lung cancer is shown in *Figure 1*. Image guided radiation therapy is delivered by use of CBCT to localize the target and make appropriate shifts prior to each treatment. Respirtory motion is monitored using the RPM system (Varian Medical Systems, Inc, Palo Alto, CA). Other systems, such as VisionRT (Varian Medical Systems, Inc) are currently under development as alternatives to the RPM system.

Early clinical experience with SBRT

Following early pioneering reports on stereotactic treatments primarily of liver and lung tumors (47,48), a phase I study by Timmerman *et al.* reported the results of 37 medically inoperable patients treated with SRT. The maximum tumor size was 7 cm, and all patients were treated using a rigid immobilization frame along with abdominal pressure. Gross tumor volume (GTV) was expanded by 0.5 cm radially and 1.0 cm cranio-caudally to create PTV. Three fractions were delivered, starting with 8 Gy to the 80% isodose line with increases up to 22 Gy per fraction. The maximum tolerated dose (MTD) was not reached in this series. With median

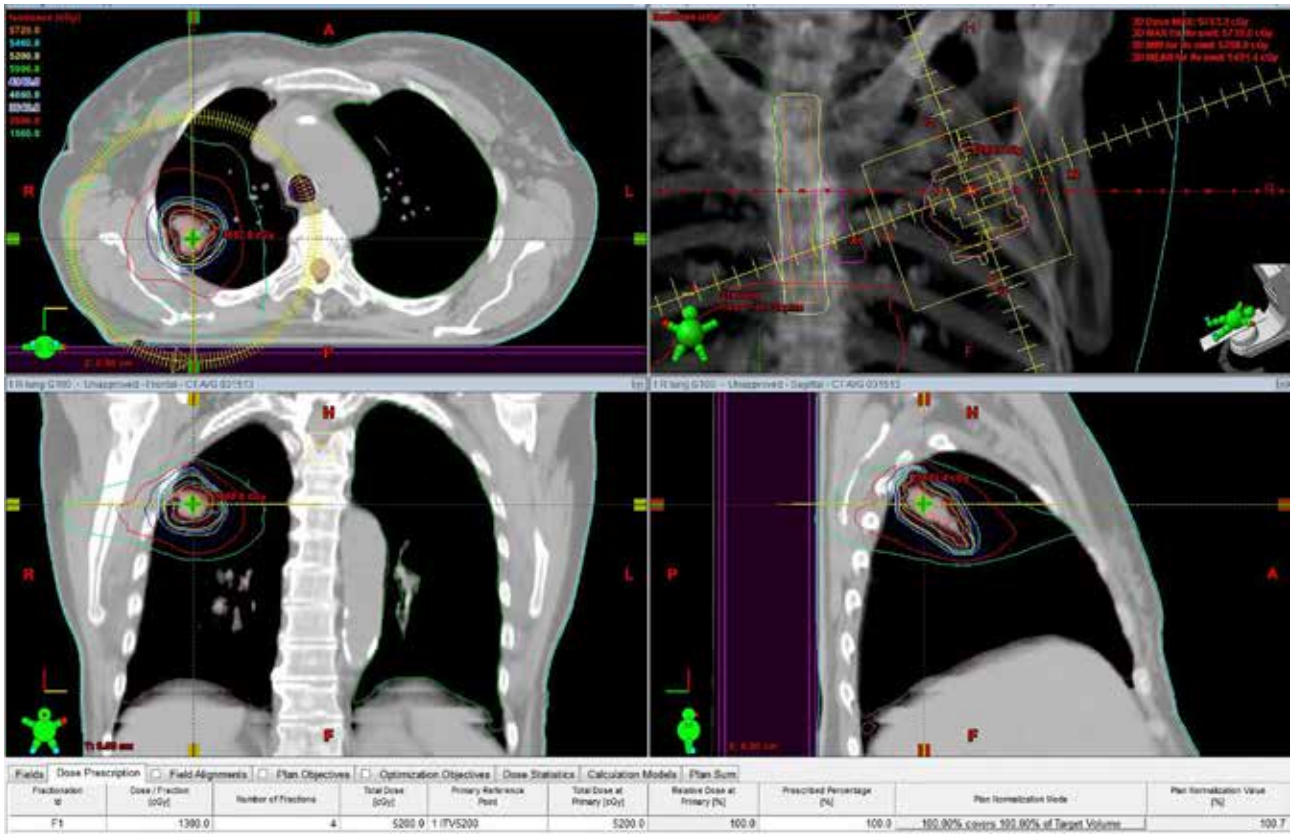


Figure 1 Representative treatment plan of SBRT of a right upper lobe lesion. Target volume was 49 cm^3. The prescription dose to the PTV was 5,600 cGy in 4 fractions. Illustrated are multiple techniques to improve coverage including 3D planning, Volumetric Modulated Arc Therapy (VMAT), and collimation of a multileaf collimator. SBRT, stereotactic body radiotherapy.

follow up of 15.2 months, there were two instances of acute grade three lung toxicity and no instances of late lung toxicity reported. The overall response rate was 87%. There were six patients with local failure, two of which also failed distantly; no patient treated with fraction sizes of >18 Gy experienced local failure (49). This experience was subsequently updated, now including 47 total patients. MTD had still not been reached for patients with T1 tumors, however three of five patients with T2 tumors larger than 5 cm experienced grade three or higher toxicity at the 72 Gy dose level. The MTD for these patients was therefore 66 Gy (22 Gy ×3 fractions). Of ten local failures, nine were seen in patients treated with <16 Gy per fraction (50).

Based on these encouraging results, a phase II investigation was undertaken and published in 2006. This series included 70 medically inoperable patients with stage T1N0 (n=35) or T2N0 (n=35) non-small cell lung cancer (NSCLC) treated with 3 fractions of 20 or 22 Gy, respectively, in the same manner as above. With median follow up of 17.5 months, two year local control was 95%. Unfortunately, eight patients had experienced grade 3-4 toxicity; there were also a total of six grade 5 toxicities, occurring from 0.6 to 19.5 months post-treatment. Four of these were due to pneumonia, while the patient who experienced death at 19.5 months died as a result of massive hemoptysis. The authors advised caution when treating patients with centrally located tumors due to the observed increase in toxicity (51). Reports from other institutions have supported the finding of increased toxicity for central tumors. RTOG 0813 is a phase I/II study that is looking specifically at centrally located tumors and is looking at dose escalation of 5 fractions delivered over 1.5-2 weeks. The study started at 50 Gy in 5 fractions and had gotten to 12 Gy per fraction, but preliminary reports are showing some increased toxicity at that level. Final results have not been reported, but will most likely recommend doses in the range of 10-11 Gy per fraction with total doses of 50-55 Gy.

RTOG 0236 was designed to mirror the single-

institution phase II study at the University of Florida detailed above. Patients enrolled on this phase II study were to receive a total of 60 Gy in three 20 Gy fractions. Patients with tumors of the proximal bronchial tree were excluded from this experience. While a 3D coordinate system was required, implanted fiducial markers were accepted as a replacement for external fixation. Treatment margins were as above. They found 3-year tumor control of 98%, 3-year local control of 91% and 3-year loco-regional control of 87%. Median overall survival was 48 months and there was a 17% grade 3-4 toxicity rate with no grade 5 toxicity (52).

Reports from overseas have also been encouraging. A large retrospective Japanese series included a total of 275 patients with stage T1N0 (n=164) or T2N0 (n=93) lung cancer were treated with a range of doses, from 18-75 Gy given in 1-22 treatment fractions. This series reported excellent outcomes, particularly those who received a biological equivalent dose (BED) of more than 100. Local failure occurred in 8.1% of those patients treated to a BED of >100 Gy, and the 5-year overall survival of operable patients in this high-dose group was 71%. This compares to a 5-year overall survival of 30% for operable patients treated to lower doses (53).

Based off these findings, the Japan Clinical Oncology Group opened a phase II trial of operable patients using a dose fractionation scheme of 48 Gy in 4 fractions. They enrolled 64 patients and showed an overall survival of 76% with 6.1% grade 3 toxicity rate with no grade 4 or 5 toxicity. In parallel, the RTOG launched 0618 and closed to accrual in May 2010 meeting their goal of 33 patients. They used 18 Gy in three fractions and limited the study to peripheral lesions. They reported their findings at the 2013 ASCO annual meeting and reported a 16% grade three toxicity rate with no grade four or five toxicity. They showed a 2-year tumor control rate of 92.3%, a regional control rate of 88.3% and a distant failure rate of 15.4%. Two-year overall survival was 84.4%. An ASOSOG/RTOG joint trial attempted a Phase III study direction comparing sublobar resection with SBRT in high risk patients with stage I NSCLC. Unfortunately, after 2 years, the study had only accrued 10% of its target of 422 patients and closed in May 2013.

In Germany, a parallel experience using single fraction treatment was reported by Fritz *et al.* Maximal tumor size was <10 cm and central lesions were excluded. Thirty-seven of 40 treated patients were medically inoperable. A rigid stereotactic frame was used, but abdominal compression was not. Patients received CT scans at end-inhalation, end-expiration, and mid-cycle. Expansions to PTV were larger, at 15 mm cranio-caudally and 10 mm radially. Dose to the isocenter was 30 Gy, with at least 80% coverage of the PTV. All patients responded to treatment, with 47.5% showing radiographic complete response (CR). There were a total of three local recurrences, giving an actuarial local control of 81% at 3 years. Asymptomatic radiation pneumonitis was seen in 75%, and transient pleural effusions in 25% of patients. The only reported grade four toxicities were rib fracture in 5% of patients (54). The RTOG has opened a phase II trial comparing the German *vs.* the Japanese fractionation scheme in RTOG 0915. They are looking at stage I peripheral tumors who will receive either 34 Gy in a single fraction (arm 1) or 48 Gy in four once daily consecutive fractions (arm 2). The primary objective was to assess toxicity of the two fractionation schemes. Accruing 94 patients they reported in 2013 that adverse events were similar (P=0.337) as was local control (97.1% and 97.6%, respectively) and concluded that 34 Gy in 1 fractions would be used as the experimental arm in a planned phase III trial (55).

Future directions of study

One common scenario in the work up of a newly identified suspicious lung lesion is the lack of a pathology-confirming biopsy. In patients with advanced obstructive and/or restrictive lung disease the morbidity of biopsy may outweigh the need for tumor confirmation. Bradley *et al.* reported a series of 91 patients treated with SBRT, of which 24% were treated without biopsy-proven NSCLC (56). They observed no difference in local control between patients with *vs.* without biopsy proven NSCLC. Also, Verstegen *et al.* compared patients with *vs.* without biopsy proven NSCLC treated with SBRT and observed no difference in local control or overall survival (57). At our institution, we recently reported on a series of 55 patients treated with SBRT, 23 without pathologic tumor confirmation. With 24 months of median follow-up, within the group without tumor verification we found an 8.7% local failure rate and a 12-month overall survival of 83%. On Kaplan-Meier analysis there was no significant difference in overall survival between the patients with and without pathologic confirmation of malignancy (P=0.27) (58). Obviously, larger prospective studies will need to be accomplished to more accurately show the validity of treatment in patients without confirmed NSCLC. Likewise, SBRT appears to be a safe and effective alternative in elderly patients over 80 years old (59).

Another scenario where SBRT may play an important

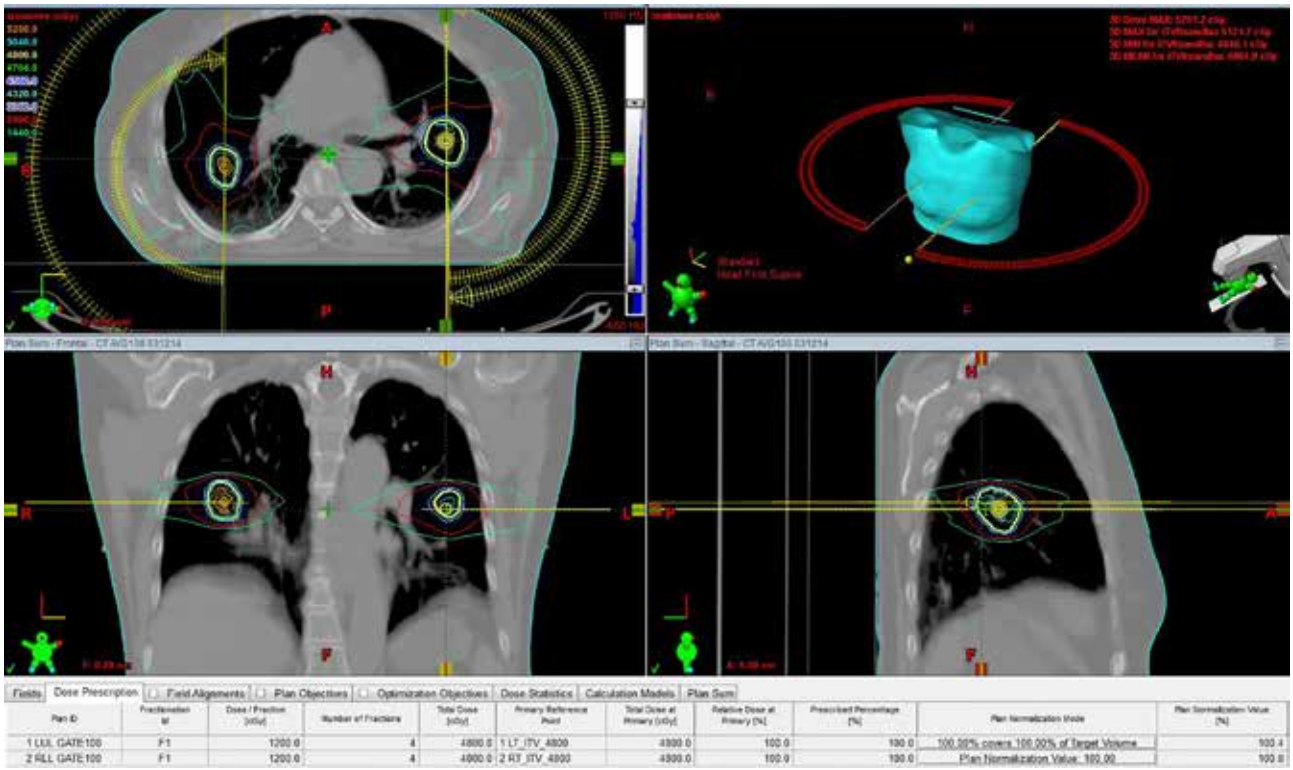


Figure 2 Representative treatment plan of SBRT for synchronous primaries, one in the right upper lobe and a second in the left upper lobe. Two separate isocenters were used with separate gating of each lesion. Prescription dose was 4,800 cGy to each lesion. Point max dose constraints to the spinal cord (26 Gy, 6.5 Gy/fx), Chest Wall (30 Gy, 7.5 Gy/fx), Esophagus (30 Gy, 7.5 Gy/fx) and Heart (34 Gy, 8.5 Gy/fx) were achieved. SBRT, stereotactic body radiotherapy.

role is in the identification of multiple synchronous or metachronous primary lung cancers (MPLC). There is ample evidence that surgical resection remains the primary modality of treatment of these patients (60-62), but often, these patients are not surgical candidates. Given the high relative risk of smokers that will be screened based on recent US task force recommendations, multiple synchronous tumors may increase from its current rate of 1% to 4% of current lung cancer diagnoses (63). We recently reported on a series of 18 patients with 36 separate MPLC lesions. A total of 16 were not surgical candidates and 2 had refused surgery. At a median follow up of 20 months we observed local control of 81.5% with overall survival at 2 years of 62%. Grade 3 pneumonitis occurred in 17% of patients, all successfully treated with steroid therapy (64). *Figure 2* is an example of a plan to treat multiple primaries.

The role of SBRT to oligometastatic disease in the lung remains another area of active research. To date, the literature consists of retrospective, single institutional reviews. Results have been encouraging with good local control and 2- to 3-year survival (65-68).

Conclusions

SBRT is being widely adopted as definitive treatment for patients with inoperable early stage NSCLC. While more technically challenging, techniques to compensate for motion management and tumor identification are allowing more accurate and tighter treatment fields. Specific dosing and fractionation schemes are not standardized, but some caution should be used for centrally located tumors. Current studies continue to evaluate 1-, 3-, 4- and 5-fraction schedules. Safety, local control and even impact on survival have been encouraging. There are emerging studies on the role of SBRT in operable patients and an interest in comparing surgical resection with this novel treatment. Whether these comparisons will reach target accrual goals remains to be seen. Finally, SBRT may have unique benefits in treating patients unable to undergo biopsy, and in the setting of multifocal, recurrent and oligometastatic disease.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. American Cancer Society. Cancer Facts & Figures 2014. Atlanta: American Cancer Society; 2014.
2. Bach PB, Jett JR, Pastorino U, et al. Computed tomography screening and lung cancer outcomes. JAMA 2007;297:953-61.
3. International Early Lung Cancer Action Program Investigators, Henschke CI, Yankelevitz DF, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763-71.
4. Pierce JP, Messer K, White MM, et al. Prevalence of heavy smoking in California and the United States, 1965-2007. JAMA 2011;305:1106-12.
5. Jemal A, Simard EP, Dorell C, et al. Annual Report to the Nation on the Status of Cancer, 1975-2009, featuring the burden and trends in human papillomavirus(HPV)-associated cancers and HPV vaccination coverage levels. J Natl Cancer Inst 2013;105:175-201.
6. Olaussen KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 2006;355:983-91.
7. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
8. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
9. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710-7.
10. Naruke T, Goya T, Tsuchiya R, et al. Prognosis and survival in resected lung carcinoma based on the new international staging system. J Thorac Cardiovasc Surg 1988;96:440-7.
11. Smythe WR; American College of Chest Physicians. Treatment of stage I non-small cell lung carcinoma. Chest 2003;123:181S-187S.
12. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
13. Kopp R, Weidenhagen R, Reinmiedl J, et al. Outcome following lung resections for pT1 non-small cell lung cancer. Eur J Surg Oncol 2006;32:329-34.
14. Dosoretz DE, Galmarini D, Rubenstein JH, et al. Local control in medically inoperable lung cancer: an analysis of its importance in outcome and factors determining the probability of tumor eradication. Int J Radiat Oncol Biol Phys 1993;27:507-16.
15. Dosoretz DE, Katin MJ, Blitzer PH, et al. Medically Inoperable Lung Carcinoma: The Role of Radiation Therapy. Semin Radiat Oncol 1996;6:98-104.
16. Sibley GS. Radiotherapy for patients with medically inoperable Stage I nonsmall cell lung carcinoma: smaller volumes and higher doses--a review. Cancer 1998;82:433-8.
17. Slotman BJ, Antonisse IE, Njo KH. Limited field irradiation in early stage (T1-2N0) non-small cell lung cancer. Radiother Oncol 1996;41:41-4.
18. Perez CA, Pajak TF, Rubin P, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. Cancer 1987;59:1874-81.
19. Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in unresectable non-small cell lung carcinoma. Lung Cancer 1994;10 Suppl 1:S239-44.
20. Bradley J, Graham MV, Winter K, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys 2005;61:318-28.
21. PL03.05 An intergroup randomized phase III comparison of standard-dose (60 Gy) vs high-dose (74 Gy) chemoradiotherapy (CRT) +/- cetuximab (cetux) for stage III non-small cell lung cancer (NSCLC): results on cetux from RTOG 0617. Clin Adv Hematol Oncol 2014;12:2-4.
22. Hayman JA, Martel MK, Ten Haken RK, et al. Dose escalation in non-small-cell lung cancer using three-dimensional conformal radiation therapy: update of a phase I trial. J Clin Oncol 2001;19:127-36.
23. Rosenzweig KE, Fox JL, Yorke E, et al. Results of a phase I dose-escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable nonsmall cell lung carcinoma. Cancer 2005;103:2118-27.
24. Emami B, Mirkovic N, Scott C, et al. The impact of regional nodal radiotherapy (dose/volume) on regional progression and survival in unresectable non-small cell

lung cancer: an analysis of RTOG data. Lung Cancer 2003;41:207-14.
25. Rosenzweig KE, Sim SE, Mychalczak B, et al. Elective nodal irradiation in the treatment of non-small-cell lung cancer with three-dimensional conformal radiation therapy. Int J Radiat Oncol Biol Phys 2001;50:681-5.
26. Martel MK, Ten Haken RK, Hazuka MB, et al. Estimation of tumor control probability model parameters from 3-D dose distributions of non-small cell lung cancer patients. Lung Cancer 1999;24:31-7.
27. Cox JD, Pajak TF, Asbell S, et al. Interruptions of high-dose radiation therapy decrease long-term survival of favorable patients with unresectable non-small cell carcinoma of the lung: analysis of 1244 cases from 3 Radiation Therapy Oncology Group (RTOG) trials. Int J Radiat Oncol Biol Phys 1993;27:493-8.
28. Machtay M, Hsu C, Komaki R, et al. Effect of overall treatment time on outcomes after concurrent chemoradiation for locally advanced non-small-cell lung carcinoma: analysis of the Radiation Therapy Oncology Group (RTOG) experience. Int J Radiat Oncol Biol Phys 2005;63:667-71.
29. Machtay M, Washam C, Devine P. Pilot study of accelerated radiotherapy with concurrent chemotherapy for stage III non-small cell lung cancer. Semin Oncol 2005;32:S9-12.
30. De Ruysscher D, Wanders R, van Haren E, et al. HI-CHART: a phase I/II study on the feasibility of high-dose continuous hyperfractionated accelerated radiotherapy in patients with inoperable non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;71:132-8.
31. Saunders M, Dische S, Barrett A, et al. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. Radiother Oncol 1999;52:137-48.
32. Brodin O, Lennartsson L, Nilsson S. Single-dose and fractionated irradiation of four human lung cancer cell lines in vitro. Acta Oncol 1991;30:967-74.
33. Carmichael J, Degraff WG, Gamson J, et al. Radiation sensitivity of human lung cancer cell lines. Eur J Cancer Clin Oncol 1989;25:527-34.
34. Guckenberger M, Baier K, Guenther I, et al. Reliability of the bony anatomy in image-guided stereotactic radiotherapy of brain metastases. Int J Radiat Oncol Biol Phys 2007;69:294-301.
35. Hoogeman MS, Nuyttens JJ, Levendag PC, et al. Time dependence of intrafraction patient motion assessed by repeat stereoscopic imaging. Int J Radiat Oncol Biol Phys 2008;70:609-18.
36. Wulf J, Hädinger U, Oppitz U, et al. Stereotactic radiotherapy of extracranial targets: CT-simulation and accuracy of treatment in the stereotactic body frame. Radiother Oncol 2000;57:225-36.
37. Purdie TG, Bissonnette JP, Franks K, et al. Cone-beam computed tomography for on-line image guidance of lung stereotactic radiotherapy: localization, verification, and intrafraction tumor position. Int J Radiat Oncol Biol Phys 2007;68:243-52.
38. Herfarth KK, Debus J, Lohr F, et al. Extracranial stereotactic radiation therapy: set-up accuracy of patients treated for liver metastases. Int J Radiat Oncol Biol Phys 2000;46:329-35.
39. Cheung PC, Sixel KE, Tirona R, et al. Reproducibility of lung tumor position and reduction of lung mass within the planning target volume using active breathing control (ABC). Int J Radiat Oncol Biol Phys 2003;57:1437-42.
40. Hanley J, Debois MM, Mah D, et al. Deep inspiration breath-hold technique for lung tumors: the potential value of target immobilization and reduced lung density in dose escalation. Int J Radiat Oncol Biol Phys 1999;45:603-11.
41. Jiang SB. Technical aspects of image-guided respiration-gated radiation therapy. Med Dosim 2006;31:141-51.
42. Wurm RE, Gum F, Erbel S, et al. Image guided respiratory gated hypofractionated Stereotactic Body Radiation Therapy (H-SBRT) for liver and lung tumors: Initial experience Acta Oncol 2006;45:881-9.
43. Shimizu S, Shirato H, Ogura S, et al. Detection of lung tumor movement in real-time tumor-tracking radiotherapy. Int J Radiat Oncol Biol Phys 2001;51:304-10.
44. Murphy MJ. Tracking moving organs in real time. Semin Radiat Oncol 2004;14:91-100.
45. Rangaraj D, Papiez L. Synchronized delivery of DMLC intensity modulated radiation therapy for stationary and moving targets. Med Phys 2005;32:1802-17.
46. D'Souza WD, Naqvi SA, Yu CX. Real-time intra-fraction-motion tracking using the treatment couch: a feasibility study. Phys Med Biol 2005;50:4021-33.
47. Blomgren H, Lax I, Näslund I, et al. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 1995;34:861-70.
48. Nádvorník P, Kolarík J, Bolf J. First model of whole body computerized stereotactic device. Acta Univ Palacki Olomuc Fac Med 1989;121:149-52.

49. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. Chest 2003;124:1946-55.
50. McGarry RC, Papiez L, Williams M, et al. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. Int J Radiat Oncol Biol Phys 2005;63:1010-5.
51. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
52. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
53. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100.
54. Fritz P, Kraus HJ, Blaschke T, et al. Stereotactic, high single-dose irradiation of stage I non-small cell lung cancer (NSCLC) using four-dimensional CT scans for treatment planning. Lung Cancer 2008;60:193-9.
55. Videtic G, Hu C, Singh A, et al. Radiation Therapy Oncology Group (RTOG) Protocol 0915: A Randomized Phase 2 Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients With Stage I Peripheral Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2013;87:S3.
56. Bradley JD, El Naqa I, Drzymala RE, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung cancer: the pattern of failure is distant. Int J Radiat Oncol Biol Phys 2010;77:1146-50.
57. Verstegen NE, Lagerwaard FJ, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy following a clinical diagnosis of stage I NSCLC: comparison with a contemporaneous cohort with pathologically proven disease. Radiother Oncol 2011;101:250-4.
58. Haidar YM, Rahn DA 3rd, Nath S, et al. Comparison of outcomes following stereotactic body radiotherapy for non-small cell lung cancer in patients with and without pathological confirmation. Ther Adv Respir Dis 2014;8:3-12.
59. Sandhu AP, Lau SK, Rahn D, et al. Stereotactic body radiation therapy in octogenarians with stage I lung cancer. Clin Lung Cancer 2014;15:131-5.
60. Carretta A, Ciriaco P, Melloni G, et al. Surgical treatment of multiple primary adenocarcinomas of the lung. Thorac Cardiovasc Surg 2009;57:30-4.
61. Chang YL, Wu CT, Lee YC. Surgical treatment of synchronous multiple primary lung cancers: experience of 92 patients. J Thorac Cardiovasc Surg 2007;134:630-7.
62. Rea F, Zuin A, Callegaro D, et al. Surgical results for multiple primary lung cancers. Eur J Cardiothorac Surg 2001;20:489-95.
63. Verhagen AF, Tavilla G, van de Wal HJ, et al. Multiple primary lung cancers. Thorac Cardiovasc Surg 1994;42:40-4.
64. Rahn D, Thakur S, Makani S, et al. Stereotactic body radiation therapy (SBRT) for multiple primary lung cancers (MPLC): a review and case series. Journal of Radiosurgery & SBRT 2013;2:135.
65. Navarria P, Ascolese AM, Tomatis S, et al. Stereotactic body radiotherapy (sbrt) in lung oligometastatic patients: role of local treatments. Radiat Oncol 2014;9:91.
66. Singh D, Chen Y, Hare MZ, et al. Local control rates with five-fraction stereotactic body radiotherapy for oligometastatic cancer to the lung. J Thorac Dis 2014;6:369-74.
67. Filippi AR, Badellino S, Guarneri A, et al. Outcomes of single fraction stereotactic ablative radiotherapy for lung metastases. Technol Cancer Res Treat 2014;13:37-45.
68. Baschnagel AM, Mangona VS, Robertson JM, et al. Lung metastases treated with image-guided stereotactic body radiation therapy. Clin Oncol (R Coll Radiol) 2013;25:236-41.

Cite this article as: Davis SW, Rahn DA III, Sandhu AP. Stereotactic body radiation therapy (SBRT) for non-small cell lung cancer (NSCLC): current concepts and future directions. Transl Cancer Res 2014;3(4):303-312. doi: 10.3978/j.issn.2218-676X.2014.07.02

Future Direction

Stereotactic ablative radiotherapy (SABR) for lung cancer: what does the future hold?

Billy W Loo Jr

Radiation Oncology and Thoracic Radiation Oncology Program, Department of Radiation Oncology, Stanford University and Cancer Institute, Stanford, CA, USA

Corresponding to: Billy W Loo Jr, MD, PhD. Department of Radiation Oncology, Stanford University and Cancer Institute, 875 Blake Wilbur Drive, Stanford, CA 94305, USA. Email: bwloo@stanford.edu.

Submitted Jun 30, 2011. Accepted for publication Jun 30, 2011.
doi: 10.3978/j.issn.2072-1439.2011.06.08
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2011.06.08

While radiation therapy has long been one of the pillars of therapy for potentially curable stages of lung cancer, outcomes have largely remained disappointing overall. The best outcomes in lung cancer have been achieved with surgery and only in early stage disease, because in early stages complete tumor ablation by surgery is possible in most patients who can tolerate the appropriate resection (lobectomy). Even so, many patients with anatomically resectable early lung cancer are not treated with surgery: in the United States, up to over one third of such patients do not have surgery for reasons including older age and multiple comorbidities (1). Conventional radiation therapy, while modestly effective, does not approach surgical cure rates because it has not been possible or practical to achieve ablative radiation dose intensities tolerably using such techniques (2).

In under two decades, the development of stereotactic body radiation therapy (SBRT) (3), more appropriately called stereotactic ablative radiotherapy (SABR) (4), has revolutionized radiation therapy for early stage lung cancer. Advances in imaging and highly conformal and accurate radiation delivery have made possible the safe administration of truly ablative radiation doses, achieving tumor control rates similar to historical results from surgery. Furthermore, progress in SABR has served as a model of evidence-based medicine, driven by clinical research starting from single institution experiences, to retrospective analyses of multi-institutional data, to prospective clinical trials, many of which are ongoing. In this issue of Journal of Thoracic Disease, Dr. Senan and colleagues, investigators who have contributed substantially to the body of knowledge on SABR, provide a timely update of clinical outcomes and current controversies (5).

As summarized in their review, prospective clinical trials have demonstrated high (>90%) rates of primary tumor control within the irradiated target volume, and characteristic normal tissue toxicities have been described along with emerging data on their risk based on dosimetric parameters. Nevertheless, numerous questions remain about how to optimize this therapy. One complicating factor identified by the authors is that apparently similar nominal radiation dose prescriptions reported across series can represent widely varying dose intensities in reality. Future publications on SABR should use standardized dose reporting, specifying how targets were defined, the dose to both the periphery and center of the target, dose conformity, and the type of dose calculation algorithm. Particularly in the lung, algorithms that do not accurately model radiation interactions in tissues of heterogeneous density should be phased out because of their unpredictable and potentially large misrepresentation of actual dose delivered (6). Similarly, standardization of how local progression is assessed and distinguished from treatment-related pulmonary changes will be important. With respect to treatment without a pathologic diagnosis, several studies now strongly suggest that this can be justified when indicated by inability to safely obtain a tissue diagnosis and judicious interpretation of clinical and radiographic characteristics and demographic context. However, in the era of molecular and genetic prognostic/predictive biomarkers and therapeutics, which will undoubtedly be integrated with SABR in the future, every attempt should

be made to enroll patients on prospective trials and obtain histological and molecular characterization of their tumors, which will ultimately inform personalized therapy. The authors note furthermore that quality assurance of this technically complex and challenging treatment modality is critical to its success outside of premier academic institutions. Encouragingly, the landmark Radiation Therapy Oncology Group (RTOG) 0236 trial (7) achieved excellent results with the participation of many community centers by mandating an extensive credentialing process, effectively teaching many centers proper SABR techniques prior to their participation and highlighting the importance of credentialing and expert oversight.

In the immediate future, prospective clinical trials will help answer some of the current questions on how best to administer SABR. With respect to optimal dosing regimens, the recently completed RTOG 0915 trial compared a single dose of 34 Gy to 48 Gy in 4 fractions in medically inoperable patients with peripheral tumors, and the less toxic regimen will then be compared to the intensive 54 Gy/3 fractions regimen standardized by RTOG 0236. For central tumors, the ongoing RTOG 0813 phase I trial for centrally located tumors is designed to determine the maximum tolerated dose in 5 fractions to refine the development of risk-adapted dosing strategies (8). Most studies of SABR to date have focused on the medically inoperable population, but given the promising outcomes in those patients as well as suggested by retrospective analysis of series including potentially operable patients (9), SABR for operable patients is obviously of interest. The Japan Clinical Oncology Group (JCOG) 0403 phase II trial of SABR for peripheral operable stage IA lung cancer preliminarily found 3-year primary tumor control of 86% and overall survival of 76% in patients with a median age of 79 years (10), quite comparable to historical surgical outcomes, with final results pending. RTOG 0618, a phase II trial of SABR for peripheral operable stage I lung cancer successfully completed accrual in 2010 and results are pending.

Despite encouraging results of SABR, conducting randomized trials between lobectomy and SABR in standard risk operable patients is challenging partly because of the perception by many physicians, particularly surgeons, of lack of equipoise between the treatments, and partly because acceptance of randomization by patients is poor when the treatments seem so different in nature. Although low accrual unfortunately led to the premature closure of a randomized trial in the Netherlands (the ROSEL trial), an international randomized trial of lobectomy vs. SABR using the CyberKnife platform (the Lung Cancer STARS trial) remains open. Recognizing these difficulties, the American College of Surgeons Oncology Group (ACOSOG) and RTOG have recently opened, with strong thoracic surgery and radiation oncology support, the phase III trial ACOSOG Z4099/RTOG 1021 for high risk operable patients with peripheral stage I lung cancer who can tolerate limited surgery but not lobectomy, randomizing between less invasive sublobar resection and SABR, which might be perceived to be less dissimilar in nature and efficacy. Given the high primary tumor control rates of SABR, the main pattern of relapse is distant, with an approximately 20% rate of metastatic dissemination across multiple series (11). The Cancer and Leukemia Group B (CALGB) and RTOG have thus proposed a randomized trial of SABR for larger (2-5 cm) tumors with or without adjuvant chemotherapy to evaluate whether systemic therapy can improve progression-free survival as it does after surgery (12). Finally, combination of SABR with agents directed at radiobiological mechanisms underlying resistance to SABR such as tumor hypoxia will be an important research direction (13).

In the longer term, two important trends promise to have major implications for SABR in lung cancer: "age shift" and "stage shift." First, over at least the next two decades, the aging of the population worldwide will lead to a substantially higher absolute burden of cancer, including lung cancer. Despite the declining age-adjusted incidence of lung cancer in countries such as the United States, the number of patients diagnosed with lung cancer is expected to increase by about 50% by 2030 because of this demographic shift (14), and the problem will be compounded further in developing countries whose age-adjusted lung cancer incidence is still climbing because of past smoking trends. As a result, both the number of patients with lung cancer and the proportion that will not be surgical candidates because of advanced age and associated comorbidities will increase worldwide. Second, only a small proportion of lung cancer is diagnosed in localized stages, 15% in the United States (15), the main reason for the dismal 15% five-year survival for lung cancer overall in the U.S. and even lower globally. Promising results of CT screening for lung cancer from the International Early Lung Cancer Action Project (I-ELCAP) (16) and other non-randomized studies, and now evidence of lung cancer and all-cause mortality reduction from CT screening in the randomized National Lung Screening Trial (NLST) (17),

indicate that mortality from lung cancer can indeed be reduced by shifting the stage at diagnosis to more curable stages through early detection, as is the case with other common cancers. Ultimately this will likely be accomplished with a combination of CT imaging and other biomarkers such as detected in blood and bodily fluids, exhaled breath, etc. Together, these trends will result in many more patients with lung cancer being appropriate candidates for SABR, and most likely in a higher overall cure rate of lung cancer attributable at least partly to treatment with SABR.

In the words of pioneering computer scientist Alan Kay, "The best way to predict the future is to invent it." We must persist in developing early detection strategies and innovative therapies such as SABR, and methodically conduct clinical investigations to demonstrate their efficacy and optimize their application. Thanks to such efforts, we can glimpse what the future holds – despite the long history of grim outcomes the future of lung cancer therapy is finally looking brighter.

Acknowledgements

None.

Footnote

Conflict of interest: Dr Billy W. Loo Jr has received research support from Varian Medical Systems, General Electric Medical Systems, and Philips Medical Systems.

References

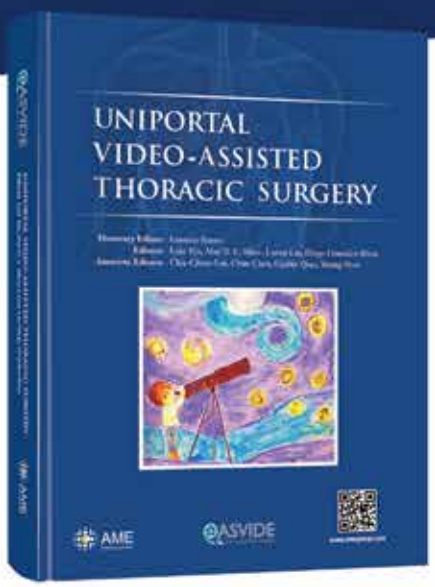
1. Cykert S, Dilworth-Anderson P, Monroe MH, Walker P, McGuire FR, Corbie-Smith G, et al. Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer. JAMA 2010;303:2368-76.
2. Qiao X, Tullgren O, Lax I, Sirzén F, Lewensohn R. The role of radiotherapy in treatment of stage I non-small cell lung cancer. Lung Cancer 2003;41:1-11.
3. Blomgren H, Lax I, Näslund I, Svanström R. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 1995;34:861-70.
4. Loo BW, Chang JY, Dawson LA, Kavanagh BD, Koong AC, Senan S, et al. Stereotactic ablative radiotherapy: what's in a name? Practical Rad Onc 2011;1:38-9.
5. Senan S, Palma DA, Lagerwaard FJ. Stereotactic ablative radiotherapy for stage I NSCLC: Recent advances and controversies. J Thorac Dis 2011;3:189-96.
6. Xiao Y, Papiez L, Paulus R, Timmerman R, Straube WL, Bosch WR, et al. Dosimetric evaluation of heterogeneity corrections for RTOG 0236: stereotactic body radiotherapy of inoperable stage I-II non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2009;73:1235-42.
7. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
8. Lagerwaard FJ, Haasbeek CJA, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;70:685-92.
9. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: Can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2010 Jul 15. [Epub ahead of print]
10. Nagata Y, Hiraoka M, Shibata T, Onishi H, Kokubo M, Karasawa K, et al. A Phase II Trial of Stereotactic Body Radiation Therapy for Operable T1N0M0 Non-small Cell Lung Cancer: Japan Clinical Oncology Group (JCOG0403) [Abstract]. Int J Radiat Oncol Biol Phys 2010;78:s27-8.
11. Chi A, Liao Z, Nguyen NP, Xu J, Stea B, Komaki R. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: Clinical implications. Radiother Oncol 2010;94:1-11.
12. NSCLC Meta-Analyses Collaborative Group, Arriagada R, Auperin A, Burdett S, Higgins JP, Johnson DH, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010;375:1267-77.
13. Brown JM, Diehn M, Loo BW. Stereotactic ablative radiotherapy should be combined with a hypoxic cell radiosensitizer. Int J Radiat Oncol Biol Phys 2010;78:323-7.
14. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol 2009;27:2758-65.
15. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin

2011;61:212-36.
16. International Early Lung Cancer Action Program Investigators, Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763-71.
17. The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. Forthcoming 2011.

Cite this article as: Loo BW Jr. Stereotactic ablative radiotherapy (SABR) for lung cancer: what does the future hold? J Thorac Dis 2011;3(3):150-2. doi: 10.3978/j.issn.2072-1439.2011.06.08

UNIPORTAL VIDEO-ASSISTED THORACIC SURGERY

Stay Calm, Think Uniportal



amazon

Honorary Editor:

Gaetano Rocco

Editors:

Lijie Tan

Alan D. L. Sihoe

Lunxu Liu

Diego Gonzalez-Rivas

Associate Editors:

Chia-Chuan Liu

Chun Chen

Guibin Qiao

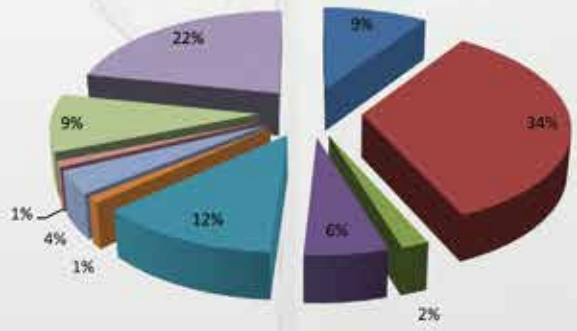
Yaxing Shen

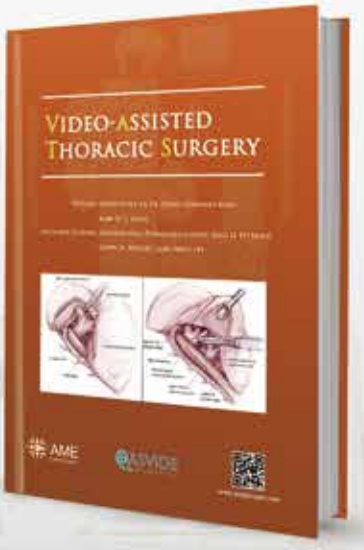
AME Publishing Company

ASVIDE AME Surgical Video Database

Video-assisted Thoracic Surgery

Editors: Jianxing He, Jie He,
Diego Gonzalez-Rivas,
Alan D. L. Sihoe
Associate Editors: Shugeng Gao, Dominique Gossot,
Rene H. Petersen, Gavin M. Wright,
Jang Ming Lee



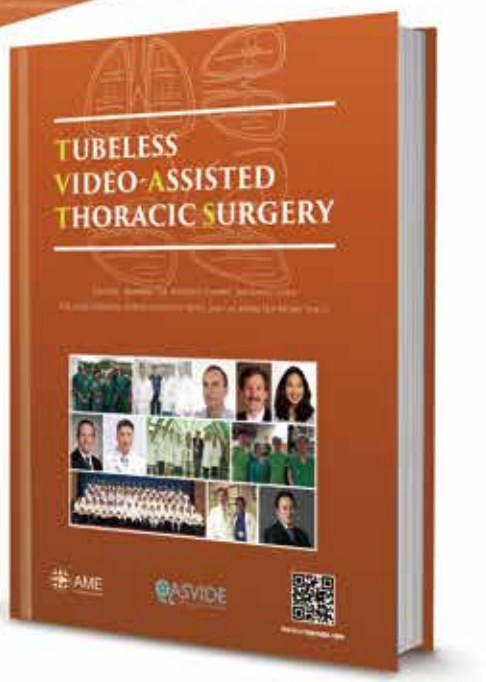


AME Publishing Company

ASVIDE AME Surgical Video Database

amazon

TUBELESS VIDEO-ASSISTED THORACIC SURGERY



NO INTUBATION

NO CHEST DRAINAGE TUBE

NO URINARY CATHETER

amazon

EDITORS:

JIANXING HE, MD, EUGENIO POMPEO, MD

JIN-SHING CHEN, MD

ASSOCIATE EDITORS:

DIEGO GONZALEZ-RIVAS, MD, JUN LIU, MD

MING-HUI HUNG, MD, YIN LI, MD

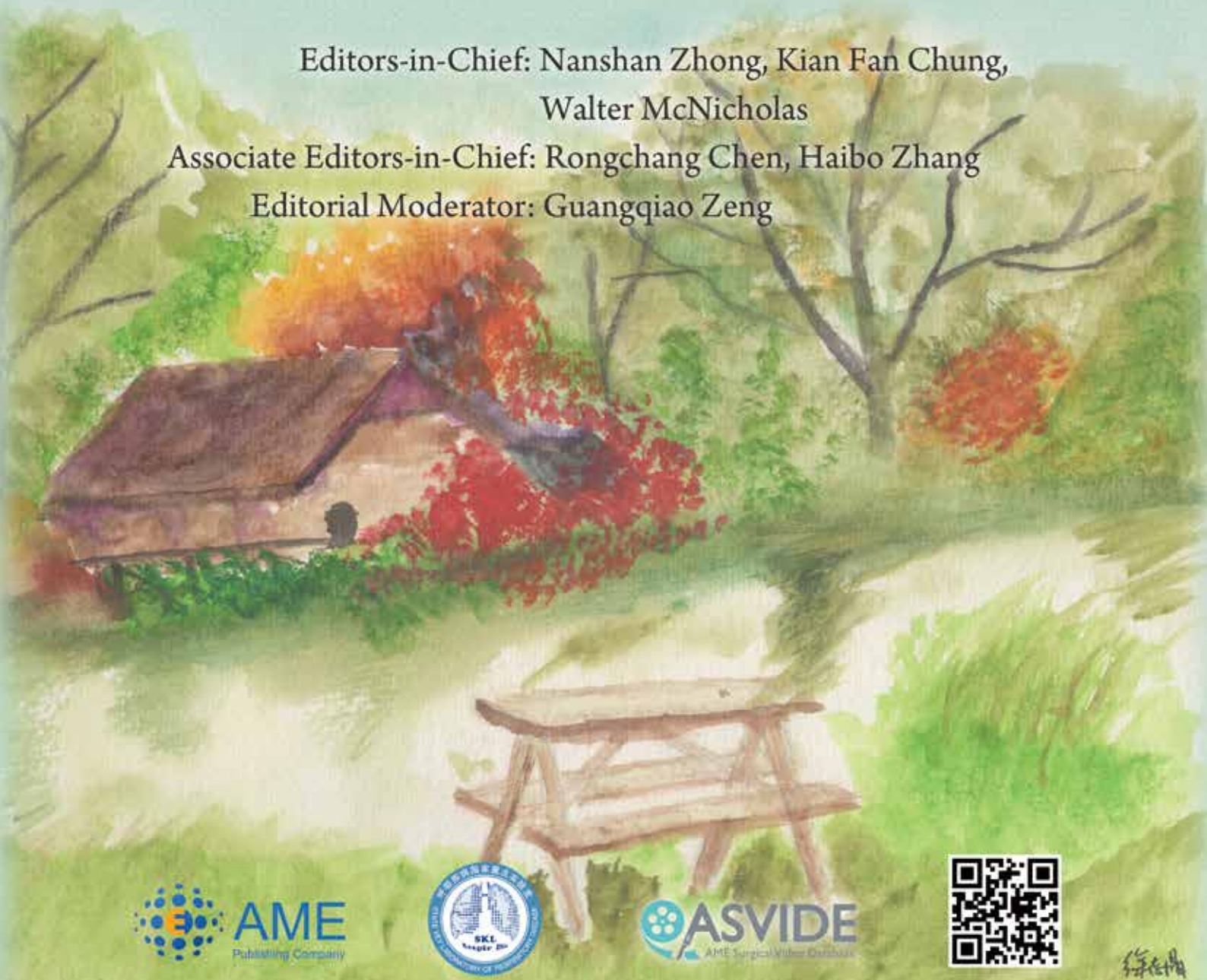
AME Publishing Company

ASVIDE AME Surgical Video Database

RESPIRATORY MEDICINE

A COLLECTION OF CLINICAL PEARLS

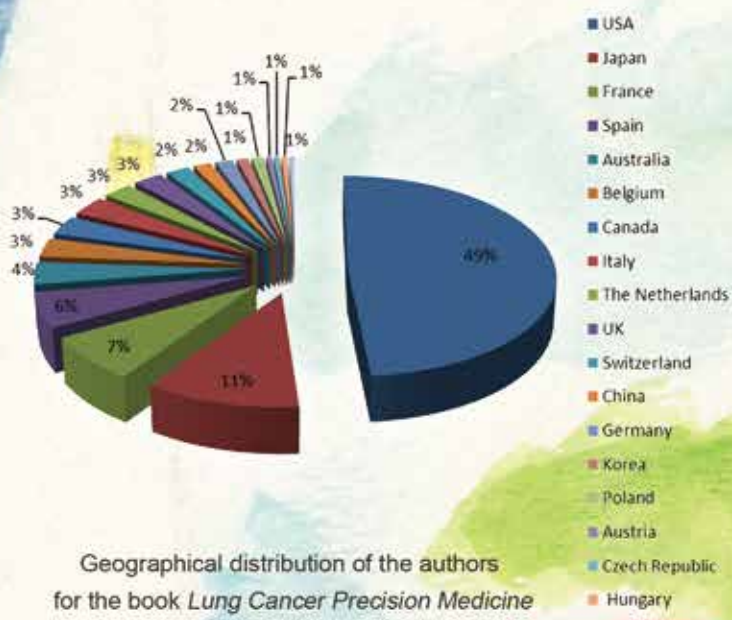
Editors-in-Chief: Nanshan Zhong, Kian Fan Chung, Walter McNicholas
Associate Editors-in-Chief: Rongchang Chen, Haibo Zhang
Editorial Moderator: Guangqiao Zeng



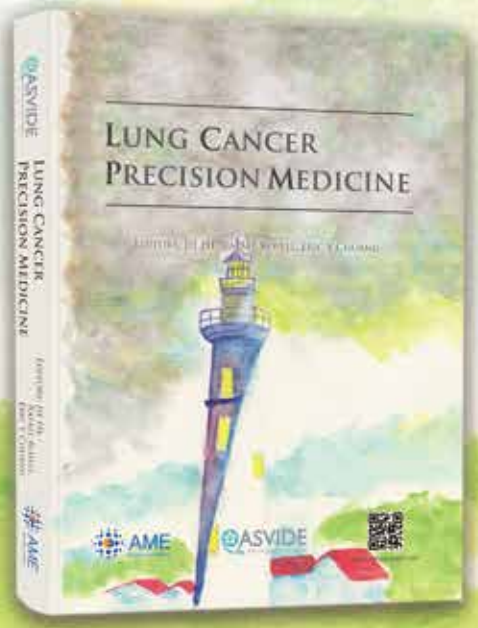
AME Publishing Company
www.amegroups.com

Lung Cancer Precision Medicine

Editors: Jie He,
Rafael Rosell,
Eric Y. Chuang



Geographical distribution of the authors for the book *Lung Cancer Precision Medicine*



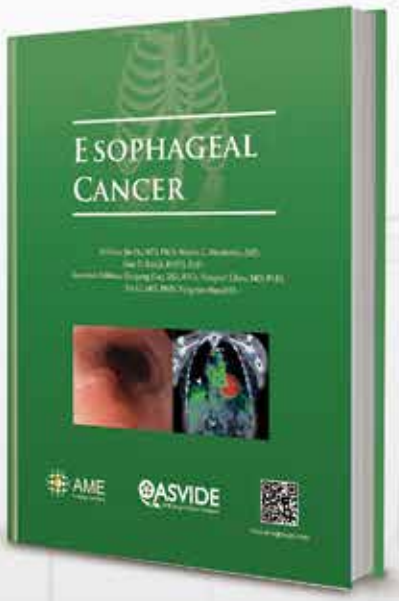
amazon

AME Publishing Company

ASVIDE
AME Surgical Video Database

AME Publishing Company

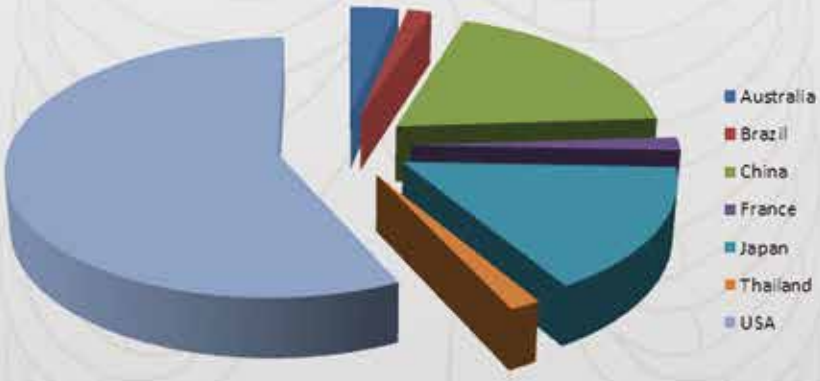
Esophageal Cancer



Editors: Jie He, MD, PhD; Wayne L. Hofstetter, MD;
Guy D. Eslick, DrPH, PhD
Associate Editors: Shugeng Gao, MD, PhD; Haiquan Chen, MD, PhD;
Yin Li, MD, PhD; Yong tao Han,MD

Contents include:

- Molecular Biology
- Overview of Diagnosis and Treatment
- Therapeutic Endoscopy
- Surgery
- Radiotherapy and Medical Treatment
- Prognosis and Prediction



来自Memorial Sloan-Kettering Cancer Center，MD Anderson Cancer Center，Duke University Medical Center, Yale University School of Medicine和Chinese National Cancer Center等众多国际著名癌症研究中心共120多位国际专家联手打造食管癌著作《Esophageal Cancer》

ASVIDE

amazon

www.amegroups.com

Particle Beam Therapy

Particle Beam Therapy: contemporary trends and reviews

Huan Giap, Eric Y Chuang, Gary Y Yang

978-988-12997-4-1 (hardback)
978-988-12997-5-8 (eBook)

hardcover, 276 pages

$ 150.00

amazon

AME Groups

Charged particles with their favorable depth of dose distribution are ideal for treating tumors located inside the body. Despite its discovery and theoretical advantages were almost 60 years ago, the clinical implementation of charged particle beam therapy has been slow due to the cost and size requirement, and its use has been limited to physics research laboratories until the last few decades. The cooperation among research laboratories, academic medical centers, and private industries has improved the technology, affordability, and ease of implementation. There has been an evolution of charged particle beam therapy over the three frontiers: technology, radiobiology and clinical outcomes.

Charged particle beam therapy: a new dawn for cancer treatment

LUNG CANCER

Honorary Editors: Jie He, Rafael Rosell, Nanshan Zhong

Editors: Jianxing He, Thomas A. D'Amico, Xiuyi Zhi

Associate Editors: Qun Wang, Tristan D. Yan, Calvin S.H. Ng, Caicun Zhou, Heather A. Wakelee, Wenhua Liang

FEATURES

- Easy access both online and in print
- With English and Chinese version
- Comprised of contributions by the most accomplished scientists and clinicians internationally
- Illustrate from the basic science of lung cancer to the most advanced therapeutic technique

AME Publishing Company

www.amegroups.com

ASVIDE AME Surgical Video Database

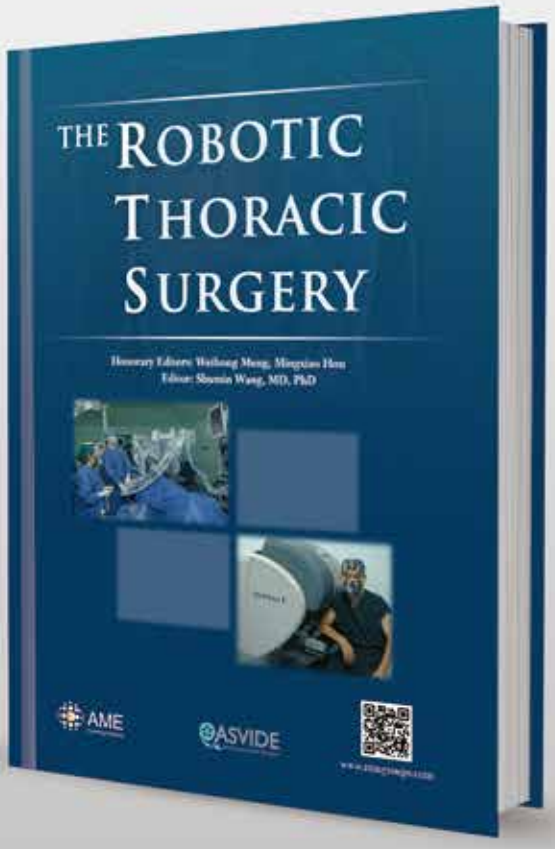
THE ROBOTIC THORACIC SURGERY

- *Pioneer in the academic arena dedicated to robotic thoracic surgery*
- *Featuring the state of the art and the international experience on robotic thoracic surgery*

Honorary Editors: Weihong Meng, Mingxiao Hou

Editor: Shumin Wang, MD, PhD

Please scan the above code for purchase information



AME Publishing Company

ASVIDE AME Surgical Video Database

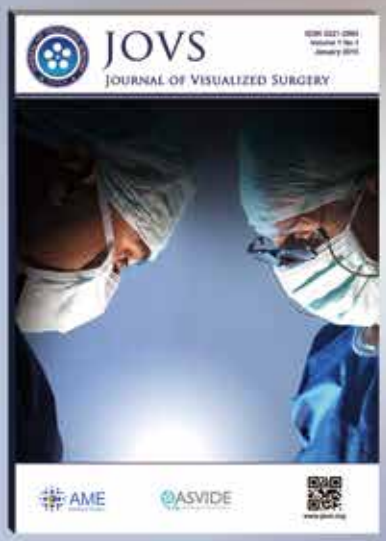
JOVS
Journal of Visualized Surgery

Features of JOVS

· Highlights the roles of each member of the multi-disciplinary surgical team

· Represents a source of the latest developments in video-enabled operations

· Serves as an archive of video instructions from the masters of such surgery from around the globe



AME Publishing Company

ATEP

ASVIDE
AME Surgical Video Database

jovs.amegroups.com

AME Journals

AME Books

AME Conferences

The 93rd annual meeting of American Association for Thoracic Surgery

Panhellenic Congress News innovation in the academic world

The 14th Central European Lung Cancer Conference (CELCC)

The 15th World Conference on Lung Cancer

The 22nd European Conference on General Thoracic Surgery

AME Database

www.amegroups.com

AME Wechat