



The more we learn, the more there is to know: the clinical management of stage I non-small cell lung cancer

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Detterbeck FC, Mase VJ Jr, Li AX, *et al.* A guide for managing patients with stage I NSCLC: deciding between lobectomy, segmentectomy, wedge, SBRT and ablation-part 2: systematic review of evidence regarding resection extent in generally healthy patients. *J Thorac Dis* 2022;14:2357-86.

Bade BC, Blasberg JD, Mase VJ Jr, *et al.* A guide for managing patients with stage I NSCLC: deciding between lobectomy, segmentectomy, wedge, SBRT and ablation-part 3: systematic review of evidence regarding surgery in compromised patients or specific tumors. *J Thorac Dis* 2022;14:2387-411.

Park HS, Detterbeck FC, Madoff DC, *et al.* A guide for managing patients with stage I NSCLC: deciding between lobectomy, segmentectomy, wedge, SBRT and ablation-part 4: systematic review of evidence involving SBRT and ablation. *J Thorac Dis* 2022;14:2412-36.

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Introduction

Lung cancer has long been classified as the leading cause of cancer-related deaths in the United States. We now have the opportunity to change this statistic through lung cancer screening programs and improving therapeutics. We are lucky there are many ways in which to treat early-stage lung cancer. However, this variety of treatment options, as well as the heterogeneity of our patient populations, raises many clinical questions. Ongoing clinical trials are encouraging, and the pace of data researchers are generating in this space offers a real chance at finding the answers for our patients. This is an exciting time to be a thoracic surgeon or anyone that treats early-stage lung cancer.

Dr. Detterbeck and his colleagues have done an incredible job summarizing the available literature on the treatment of early-stage lung cancer. They undertook this opus to create a practical guide for choosing the appropriate treatment strategy for individual patients based not only on the long-term and short-term outcomes, but also on the patient reported outcomes specific to each treatment strategy. This guide (1-4) promotes a strategy that optimizes patient outcomes as well as patient satisfaction. In this way,

we can select treatments that are both guideline concordant and goal concordant for each patient.

In this special series, “A Guide for Managing Patients with Stage I NSCLC: Deciding between Lobectomy, Segmentectomy, Wedge, SBRT, and Ablation”, practitioners can find four sections. The first guide provides a summary of the overall findings as well as an in-depth discussion of the methodology for this review series. This section describes how we might make a decision for an individual patient, balancing long-term, short-term, and intermediate outcomes, as well as highlighting the nuances (effect modifiers). This section describes a framework for decision-making which includes a shared decision-making model. The second guide provides an in-depth analysis for generally healthy patients. Because most studies focus on generally healthy subjects, this particular guide benefits from the most robust literature. The third guide focuses on specific patient categories, such as those with reduced pulmonary function tests, as well as specific types of tumors, such as ground glass opacities (GGOs). This section also highlights many of the unanswered questions for these presumably favorable tumors that are being found with increased frequency due to screening and increased

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use of CT scans for other purposes (resulting in increased numbers of incidentally found nodules). The fourth and final guide focuses on evidence for nonsurgical therapies such as stereotactic body radiotherapy (SBRT) and ablation.

First, we must congratulate the authors on this incredible and comprehensive work organizing a large volume of data on a complex topic. Based on the reference lists for each main article as well as the supplements, the authors must have reviewed close to one thousand manuscripts. They then organized the data into a partitioned series in which practitioners can easily access guidance for a particular patient. The work is summarized in tables and figures that make finding quick answers easy but also includes incredible detail that allows readers to dig in further to come to their own conclusions based on the data available. The authors did not shy away from clinical scenarios in which the literature is incomplete. Rather they attempted to offer best guidance based on the incomplete data, simultaneously highlighting areas for further investigation.

Methods

The authors organized their work around four clinical scenarios: healthy patients, older patients, patients with limited pulmonary reserve, and tumors with likely excellent long term oncologic outcomes. Within each scenario, the authors made two comparisons: (I) type/extent of resection and (II) resection versus SBRT/ablative therapy. The data for each outcome is provided along with an assessment of the quality of the recommendation and the confidence in the recommendation. Each treatment strategy is compared based on short-term (90-day), intermediate (1–2 years), and long-term (5 years) outcomes. Careful consideration was given to choosing the appropriate outcome. For example, overall survival typically has less to do with how a cancer was treated and more to do with underlying patient characteristics. For that reason, the authors tried to report data on freedom from recurrence as this oncologic outcome is more likely to be a result of the treatment strategy.

Before discussing the findings in more detail, we would like to highlight some of the methods that make this series a particularly robust guide. Because much of the data is retrospective in nature, a thorough assessment of potential bias was critical. Authors assessed confounders and assigned a reliability grade for how much confidence readers could have in the attribution of cause and effect between treatment and outcome. To assess how well confounders were considered, the authors *a priori* developed

a conceptual model to describe all potential confounders. This then allowed the authors to determine whether the individual study assessed each of those confounders. The authors used a described tool (5) for assessing the risk of bias in observational studies. They then modified this tool to reflect potential confounders relevant to stage I non-small cell lung cancer (NSCLC) specifically. The authors provide a detailed description of this adapted tool in appendix 2-1. This supplement also gives a brief description of the methods available to adjust for multiple variables in observational studies. The supplement can serve as something of a primer on evaluating and understanding the observational studies that have been published on this and other topics.

Findings

The findings are grouped into broad categories. First are generally healthy patients, next are older patients, then patients with limited pulmonary reserves, and lastly patients with potentially favorable tumors. In generally healthy patients, there are little to no differences in short-term outcomes by resection extent (wedge versus segment, versus lobe). There are differences in short term outcomes based on surgical approach. There is a significant benefit to minimally invasive approaches over thoracotomy in terms of major complications, pain, and impaired quality of life. While there are no randomized controlled trials, some well done and fully adjusted nonrandomized comparisons indicate there is worse overall survival for any type of sublobar resection when compared to lobectomy. As expected in this healthy patient population, overall survival after any nonsurgical therapy has been consistently reported as worse than after surgical resection. However, average quality of life is clearly better after radiation than surgery. This is more most clear in the short term, but also persists in the long term when compared to an open resection.

The data for older adults mirror that for generally healthy patients with a few key exceptions. In particular, patient selection for surgery is crucial; absolute age appears to be less important than patient robustness. However, measuring patient robustness, or on the flip side patient frailty, is still more of an art than a science. While morbidity is higher initially after surgery, late toxicity after radiation makes the overall incidence essentially equal after 2 years. Quality of life is worse after surgery (especially open surgery), but long-term survival is better after surgery in observational studies, even in septo- and octogenarians.

Nevertheless, as patients get older or frailer, the short-term benefits of radiation as compared to surgery are accentuated and the long-term downsides of radiation are diminished, making radiation an increasingly attractive option for these patients.

While the benefit of minimally invasive surgery is well described in all patient populations, patients with compromised pulmonary function likely see the most benefit from a minimally invasive video-assisted thoracic surgery (VATS) versus open approach to surgery. In these patients, complications double if the approach is open as compared to VATS (and by extrapolation, robotic assisted thoracic surgery). Interestingly, forced expiratory volume in 1 second (FEV1) is unchanged or even improved after a lobectomy. There is no clear difference in short-term and long-term outcomes when comparing extent of resection. It should be noted that the data to support these conclusions is quite limited. Based on current data, the extent of resection should be determined by physiologic, anatomic, and technical factors. For example, resecting a non-functional lobe (such as an emphysematous upper lobe) may improve pulmonary function. Additionally, a straightforward lobectomy or large wedge resection that can be done VATS may result in better short-term outcomes than a complex segmentectomy, especially if done via open thoracotomy. Similarly, when comparing surgery to non-surgical options, the short- and intermediate-term outcomes tend to favor non-surgical options when the surgery would involve a thoracotomy. Interstitial lung disease presents a particular problem. Many of these patients are at elevated risk of an acute exacerbation following surgery. On the other hand, these patients are at higher risk of long-term toxicity from SBRT. The treatment and management decisions for these patients is best made in a multidisciplinary setting.

The last patient population discussed in this series is those patients with a potentially favorable tumor biology [e.g., GGO or low positron emission tomography (PET) avidity]. These tumors are especially problematic in patients afflicted with multifocal adenocarcinoma, in whom doing a lobectomy for all areas of disease would result in unacceptable or nonexistent pulmonary reserve. Generally, patients with GGOs and screen-detected tumors have excellent long-term survival regardless of resection extent. However, there is increasing concern for late (>5–10 years post-resection) local recurrence in patients who have a sublobar resection. There is no data available for non-surgical therapies specifically for favorable tumor types. Pure GGOs likely do not require treatment until there is

growth of a solid component greater than two millimeters on mediastinal windows or consolidation of greater than five millimeters as seen on lung windows. Growth of the ground glass component should not be considered an indication for intervention based on best available evidence. However, the natural history of GGOs, the best treatment strategy for these tumors, and specifically for multifocal adenocarcinoma, are areas of study in desperate need of delineation.

Ongoing clinical trials

See *Table 1*. Herein we describe relevant ongoing clinical trials with their expected completion dates.

Future directions

This series highlighted many areas in which data is lacking or incomplete. First, while it is generally accepted that treatment should be in alignment with patient attitudes and goals, there is surprisingly little research into how best to understand what those goals are. This process is double faceted. For one, the process of how patients clarify and articulate their goals for themselves should be better understood. Next, we have to understand how this information is best and most efficiently communicated from patients to providers.

Second, data that is specific to robot-assisted resection is absent and thus most of our conclusions about this surgical approach is extrapolated from data specific to video assisted surgery. Because there are some crucial differences between robot assisted and video assisted thoracic surgery, it is important that we collect data specific to each methodology.

Third, the phenomenon of spread through air spaces (STAS) is being increasingly identified. A better understanding of this biological phenomenon is needed. STAS appears to have a negative effect on outcomes, but it is unclear if it is due to the STAS characteristic itself or some other related tumor biology. STAS is associated with many negative prognostic factors and delineating the effect of each is incomplete. Furthermore, it is unclear whether the extent of resection influences outcomes when STAS is present. More basic science work is needed to understand this biological behavior better and more clinical research is needed to determine how best to treat patients with this finding.

Fourth, patients with limited pulmonary function can have excellent results after surgical resection. However,

Table 1 Ongoing clinical trials defining treatment for stage I NSCLC

Trial name	Comparison	Patient population	Results anticipated/study completion
Surgical Treatment of Elderly Patients with early-stage non-small cell lung cancer (STEPS)	Sublobar vs. lobectomy	Clinical stage I, mostly solid tumors in patients aged 70 or older in China	Unclear if this trial is still accruing; the last posted update was in 2016 at which time the study was actively recruiting participants
CALGB/Alliance 140503	Sublobar (60% wedge) resection vs. lobectomy	Peripheral, mostly solid, tumors ≤ 2 cm in the US	Presented in August 2022 at the International Association for the Study of Lung Cancer World Conference suggesting that sublobar resection was not inferior to lobectomy in terms of overall survival and disease-free survival. The publication of this data is anticipated shortly
JCOG1708/SURPRISE	Sublobar vs. lobectomy	Clinical stage I, mostly solid, patients with idiopathic pulmonary fibrosis, in Japan	2029
JCOG1909/ANSWER	Wedge vs. segmentectomy	High-risk patients, clinical stage IA, in Japan	2031
JCOG1211	Segmentectomy (no comparison)	Part solid GGOs ≤ 3 cm and larger tumors (2–3 cm) predominantly GGO	2027
Veterans Affairs Lung Cancer Surgery or Stereotactic Radiotherapy (VALOR) study	SBRT vs. anatomic resection	VA patients with clinical stage I–IIA	2027
Radical Resection Vs. Ablative Stereotactic Radiotherapy in Patients With Operable Stage I NSCLC (POSTILV)	SBRT vs. resection	Clinical stage I, China	2026
STABLE-MATES	SBRT vs. sublobar resection	Clinical stage I, high risk, US	2024
HILUS	Hypofractionated SBRT to tumors 1 cm or less from the main bronchi versus all other tumors	Lung tumors, Nordic countries	Toxicity results published in 2021, survival outcomes pending
SUNSET	Hypofractionated SBRT, dosage will be continuously reassessed based on all previous data	Ultra-central T1-3N0M0, Canada	October 2022

NSCLC, non-small cell lung cancer; US, United States; GGO, ground glass opacity; SBRT, stereotactic body radiotherapy.

most of this data are based on observational studies in which there has been careful patient selection. The details of this patient selection are not clear. It would be useful to understand which patients can benefit from surgical intervention and which patients will be at risk for acute worsening of their lung disease or pulmonary complications postoperatively. In addition to understanding which patients to select for surgery, surgeons also would benefit from more

data regarding which surgery to select for their patients. While it seems clear that we should use a minimally invasive approach, the extent of resection (sublobar versus lobectomy) that would be best for these patients is not clear.

Fifth, there is no direct data for patients with favorable tumor characteristics. Because lung cancer screening programs are detecting these tumors with increasingly frequency, a better understanding of this entity is essential.

Sixth, there is limited and often conflicting evidence assessing short term outcomes after resection stratified by age or resection extent. There are ongoing randomized controlled trials comparing resection extent and one specifically in older patients. Hopefully, these studies will shed more light on this subject.

Seventh, in this series the authors included not only short-, intermediate-, and long-term outcomes, they also tried to assess differences in patient reported outcomes and quality of life metrics. However, the data in this space is quite thin. For example, there were no studies identified that addressed functional capacity or PFTs in older patients stratified by resection extent. Additionally, there was no data on pain or quality of life metrics specifically in older patients stratified by resection extent. This gap is not limited to the surgery literature. No data regarding quality of life in older patients or patients with compromised lung function who received SBRT was identified. Because these factors may be some of the most important for the patient, it is critical that we design studies with these outcomes in mind.

Lastly, our conclusions for tumors with low PET avidity or a slow growth rate are based on data for GGO tumors. Because these tumors may be distinct from each other, more specific data for each marker of low aggressiveness is necessary for complete understanding of these increasingly detected tumors.

Finally, the authors work exposes two points of recommendations for measuring and defining variables in all future studies. First, researchers should differentiate total versus solid invasive size on pathology reports for GGOs so that the natural history of these tumors can be better understood. Second, we should specify between video assisted and robot assisted resections instead of combining these all into one “minimally invasive” category. Both variable definitions likely need to occur at the data collection step rather than at the time of analysis. In many databases, this granularity has already been lost by the time researchers are accessing the data. Thus, it may be necessary to change the granularity in our nationwide databases, such as the Society of Thoracic Surgeons Database and the National Cancer Database, to reflect the true heterogeneity of clinical practice.

Conclusions

This is an exciting time to treat stage I lung cancer. While there is an incredible amount of investigation that has

been completed, we still have a great deal of work to do. Dr. Detterbeck and his colleagues undertook a massive opus in their guide for managing patients with stage I NSCLC. What has resulted is a comprehensive and well-organized discussion of all available literature on the topic. Additionally, they have highlighted areas for future investigation by identifying clinical questions that remain unanswered. This series is necessary reading for any provider who treats patients with stage one lung cancer.

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Footnote

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