Review Article

Surgical treatment for early stage non-small cell lung cancer

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Abstract: Surgery is the standard of care for early stage non-small cell lung cancer. There is significant debate about the type of operation most effective for lung cancer. Minimally invasive techniques like video-assisted (VATS) and robot-assisted thoracoscopic surgery (RATS) have been shown to reduce postoperative complications and shorten hospitalization. However, there remains skepticism about their oncologic effectiveness when compared to an open approach, though recent literature suggests no differences in upstaging or survival between VATS and thoracotomy. The extent of resection for early lung cancer also remains a matter of debate. Lobectomy remains the preferred operation and is associated with better survival and lower locoregional recurrence, but there is increased interest in the role of sublobar resections. Sublobar resections have similar mortality to lobar resections in small ground glass-predominant tumors. We examine the literature surrounding these controversies in this review.

Keywords: Lobectomy; sublobar resection; video-assisted thoracoscopic surgery (VATS); lung cancer

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Introduction

Surgery remains the standard of care for early non-small cell lung cancer (NSCLC), although a significant fraction of patients diagnosed with early lung cancer either receive no surgery or no treatment at all (1-4). There is considerable debate about the type and extent of surgery for lung cancer, which we review in this article.

Type of surgery: role of minimally invasive resections

While minimally invasive techniques such as video-assisted thoracoscopic surgery (VATS) and robot-assisted thoracoscopic surgery (RATS) have emerged in the past two decades, most lung resections continue to be performed via a thoracotomy (5).

VATS

VATS has been established as a safe and less morbid alternative to open resection, but skepticism remains about its oncologic effectiveness. When compared to lobectomy via thoracotomy, VATS has improved short-term outcomes: it is associated with a lower incidence of post-operative complications, shorter hospitalization, shorter duration of chest tube, and similar or lower rates of postoperative mortality (5-14).

Doubt persists about the oncological equivalence of VATS when compared to an open approach. Several studies have demonstrated an increase in nodal upstaging with open resection compared to VATS (12,15-17). Long-term overall and disease-free survival, however, have not been reported by these studies. Other studies have demonstrated no significant difference in upstaging between the two techniques (18-20).

The equivocal data might be explained by variables like institutional experience, learning curve, and size of tumor. The study by Medbery *et al.* found no difference in upstaging when resections were performed at an academic center, as opposed to in community practice (12). Of note, a recent large retrospective cohort study of the National Cancer Data Base (NCDB) found no difference in nodal upstaging and overall 5-year survival between patients undergoing thoracoscopic or open resections for stage I lung cancer after both multivariable modeling and propensity matching (19).

RATS

RATS is a newer technique, with the theoretical advantages of three-dimensional visualization and increased rotational capabilities ("wristedness") compared to VATS. The safety of RATS was questioned with an early study of the Nationwide Inpatient Sample (NIS) in 2014 that revealed an increased risk of cardiovascular complications and iatrogenic bleeding with RATS when compared to VATS (21); a smaller study noted less perioperative blood loss with VATS compared to RATS (22). Other studies, including more recent analyses, have found no differences in short-term outcomes between RATS and VATS, and have demonstrated improvements in immediate outcomes, such as length of stay, bleeding, duration of chest tube, and perioperative mortality, when RATS was compared to open resection (23-26). However, a significant deterrent for RATS is the increased costs associated with it (25-27). It does appear that the emergence of RATS has increased the fraction of procedures being performed minimally invasively, as opposed to thoracotomy.

There are little data about the oncologic effectiveness of RATS. One study showed increased nodal upstaging in RATS compared to VATS, while a much larger NCDB analysis showed no differences in upstaging between the minimally invasive approaches (18,28). There was no difference in two-year survival in the NCDB study. A recent single-institution retrospective study demonstrated increased number of nodal stations assessed by RATS compared to VATS, but did not report upstaging; 5-year overall and disease-free survival did not vary between the groups (13).

Extent of surgery: effectiveness of lobar and sublobar resections

Lobectomy remains the standard of care for early stage lung cancer, but sublobar resections, including non-anatomical wedge resections and anatomical segmentectomies, have generated interest given their numerous hypothetical advantages. Sublobar resections may preserve more lung function compared to lobar resections, and may be especially useful in patients with marginal pulmonary function (29,30), although the effect on lung preservation is not reported in all studies (31,32).

Many studies suggest an advantage for lobectomy over sublobar resections in terms of survival and local recurrence. The only randomized controlled trial comparing lobectomy to sublobar resections reported a threefold increase in locoregional recurrence with sublobar resections (33). A meta-analysis of 31 studies compared outcomes between lobar and sublobar resections in stage I cancer and found an overall survival advantage in lobar resections (34). This advantage disappeared in stage IA cancer and VATS procedures. Other meta-analyses have also demonstrated a survival benefit for lobectomy in stage I NSCLC while failing to reveal a significant difference in survival between lobectomy and sublobar resections for stage IA cancer with a tumor diameter less than two cm (35,36). Other studies have reported a range of results from marginal survival benefit with lobectomy (31) to clear benefit in a large population-based analysis (37-39).

On the other hand, there is also some evidence to suggest that lobectomy does not confer a significant survival benefit over sublobar resections. Two recent meta-analyses have failed to demonstrate a clear survival advantage of lobectomy over sublobar resections (30,40). Several retrospective analyses have shown no survival benefit for lobectomy over sublobar resections, especially segmentectomy, in stage IA lung cancer with a tumor diameter less than two cm (41-48). There are also data that outcomes in sublobar resections are improved with margins at least equivalent to the size of the tumor and with adequate nodal assessment (1,43).

A number of reasons could account for the equivocal data comparing lobar and sublobar resections: (I) there is often poor distinction between the types of resections defined as sublobar, which could account for heterogeneity. For instance, wedge resections may not be expected to have the same outcomes as anatomic resections (49), although the two are often grouped together in analyses; (II) the staging of lung cancer has evolved over the decades, and consequently the assessment of stage in the literature is inconsistent. For instance, there is increasing realization that less aggressive manifestations of early lung cancer, such as adenocarcinoma *in situ*, exist. These cancers are more readily identified with contemporary axial imaging

by a greater ground-glass proportion, and may be more amenable to limited resection (50-54); (III) this staging-related inconsistency can be further granulated into a size-related discrepancy. For example, several analyses group all stage I cancers together, while recent literature has clearly established a difference in outcomes between stage IA and stage IB cancer. While lobectomy might confer an overall survival benefit in stage I cancer, segmentectomy might have equivalent survival for selected patients with stage IA lung cancer (34). Unfortunately, many analyses do not adjust outcomes for the size of the tumor, likely resulting in discrepant results; (IV) there is also inherent variety in the reasons for patients undergoing sublobar resections. Traditionally, sublobar resections have been reserved for poor surgical candidates or patients with poor pulmonary function; this is often not adjusted for in retrospective analyses. Few studies have explicitly compared outcomes in patients undergoing lobectomies and those undergoing sublobar resections who would otherwise be eligible for lobectomies (45,55). These studies have not found a significant difference in outcomes between lobar and sublobar resections.

Sublobar resections do have a role in select candidates. Patients with poor pulmonary reserve who cannot tolerate a lobectomy should undergo a segmentectomy (56,57). Patients with other comorbidities prohibitive for lobectomy should also be considered for a sublobar resection (39,56,58-60). A recent study by Gulack *et al.* describes a risk score with comorbid conditions like age, functional status, smoking status, cerebrovascular disease, and chronic obstructive pulmonary disease (COPD) contributing to worse postoperative survival (59). Sublobar resections should also be considered in patients with metachronous or synchronous primary lung cancer, especially in patients with prior resections and with poor predicted remnant pulmonary reserve (56,61-69). The majority of studies examining the role of sublobar resections in multiple primary lung cancer have not found a difference in survival when compared to lobectomy (62-69). Some patients with evidence of less aggressive lung cancer, namely minimally invasive adenocarcinoma (MIA) or adenocarcinoma *in situ* (AIS), may also be candidates for sublobar resections. These tumors are identified by a lepidic histology or ground-glass appearance on computed tomography (CT), with new evidence suggesting they may also be associated with lower uptake on positron emission tomography (PET) (70). Sublobar resections of small (<2 cm) tumors with either lepidic histology or a high ground-glass component (>50%) have been associated with similar survival to lobectomy (58,70,71)

Sublobar resections should only be performed if there is confidence that adequate margins can be obtained. The NCCN guidelines recommend margins at least two centimeters in width or at least equivalent to the size of the resected tumor or nodule (56). Several studies have demonstrated an increase in local recurrence with margins narrower than two centimeters (72-75) and with margins smaller than the maximum diameter of the tumor (75).

Large randomized controlled trials are in progress that can provide greater insight into the role of sublobar resections in early lung cancer. The Japan Clinical Oncology Group and West Japan Oncology Group trial, JCOG0802/WJOG4607L, randomizes patients with invasive adenocarcinomas smaller than two centimeters to segmentectomy or lobectomy (76). The Alliance for Clinical Trials in Oncology study, CALGB 140503, assigns patients with small (<2 cm) peripheral tumors to either sublobar resection (wedge resection or segmentectomy) or lobar resection via VATS or thoracotomy (77,78). A phase II trial, JCOG0804/WJOG4507L, compares wide wedge resections to segmentectomies in small adenocarcinomas (79).

Conclusions

Surgery remains the mainstay treatment for early NSCLC, and lobectomy remains the preferred the operation for most patients with early stage lung cancer. Minimally invasive techniques such as VATS and RATS are increasingly used to perform lung resections, and while questions remain about the effectiveness of nodal assessment and upstaging of these newer techniques, the most recent literature suggest no significant differences in nodal upstaging and overall survival between VATS and open approaches. Sublobar resections should be the procedure of choice in patients with ground glass nodules if adequate margins are attained. Recent data also suggest that anatomic sublobar resections, segmentectomies, may offer equivalent outcomes to lobar resections for selected patients stage IA tumors that are smaller than two centimeters, although randomized data in this area are needed.

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Footnote

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