Advances in Surgical Techniques for Lung Cancer

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KEYWORDS

- Thoracic surgery • Non–small cell lung cancer
- Video-assisted thoracoscopic surgery • Robotic-assisted thoracoscopic surgery
- Neoadjuvant therapy • Navigational bronchoscopy

KEY POINTS

- Minimally invasive thoracoscopic surgery reduces perioperative morbidity while maintaining long-term survival.
- Parenchymal-sparing segmentectomy can offer the same oncologic benefits as lobectomy in highly selected patients with small (<2 cm) peripheral tumors.
- Increased thresholds for intervention and parenchymal-sparing techniques can reduce morbidity and avoid unnecessary procedures in patients with ground-glass opacities.

BACKGROUND

The goals of thoracic surgery for non–small cell lung cancer (NSCLC) are to achieve an R0 resection, perform an adequate nodal staging, and reduce any associated morbidity. Although these goals have been present since the first oncologic resections were performed nearly 100 years ago, the techniques by which they are achieved have evolved tremendously in the past 3 decades. Improvements have come on multiple fronts and include a transition to minimally invasive approaches, an incorporation of neoadjuvant treatment, and a greater utilization of sublobar resection. These advances have reduced the morbidity of thoracic surgery, while preserving or improving long-term survival. This review highlights the major advances in the surgical management of NSCLC and the keys to optimizing outcomes from a surgical perspective.

CURRENT OPERATIVE TECHNIQUES

The first description of a successful oncologic resection for lung cancer with a survival greater than 1 year was by Drs Evarts Graham and J.J. Singer in 1933.[1] In their original

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report, a left pneumonectomy was performed through a generous thoracotomy along with removal of the third through ninth rib from the spine to the anterior axillary line.[1] In the intervening decades, advances have been made to reduce the incision size, reduce morbidity, and improve safety. A modern open thoracotomy is typically performed with a posterior-lateral incision in the fifth intercostal space. A rib may be purposefully cut or "shingled" to allow for better access to the chest, but unless there is direct tumor invasion of the chest wall no ribs are resected. The serratus anterior and latissimus dorsi muscle may be preserved in a "muscle-sparing" technique in which they are retracted and spread between their fibers.[2] Using muscle-sparing techniques in combination with intercostal nerve blocks, discharge home on postoperative day 1 has been reported, all be it in highly selected patients.[3] Although these "open" techniques require a larger incision, they do allow the surgeon nearly unrestricted access to the lung and can facilitate identification of subtle lesions through digital palpation.

In the past 25 years the expansion of fiber-optic technology has allowed for surgery to be performed through small incisions with visualization provided by a camera or thoracoscope. Video-assisted thoracoscopic surgery (VATS) was adopted in the 1990s and steadily gained popularity in the 2000s.[4,5] In this technique a camera is inserted into the chest through a 5-mm incision; 3 or 4 additional incisions are made with the largest being up to 4 to 5 cm, which is necessary for extraction of the specimen. Although digital palpation of the lung is more challenging compared with open techniques, it is still possible to palpate almost all the parenchymal surface to identify and remove a nodule of interest. As a result, this technique is commonly used for surgical biopsy of a suspicious nodule or parenchymal process.

Numerous retrospective studies have compared VATS with traditional thoracotomy. These studies have consistently demonstrated a reduction in perioperative complications and hospital length of stay.[6–10] Several adjusted and propensity-matched analyses have demonstrated at least equivalent long-term survival.[8,9,11,12] However, the nodal dissection of N1 and N2 nodes can be more challenging using a VATS approach, and reduction in nodal harvest and upstaging has been observed in several large database series.[7,8,10,13] The impact of nodal evaluation on long-term survival also remains a controversial point given equivalent long-term survival in most large series.

In addition to VATS, robotic-assisted thoracoscopic surgery (RATS) has emerged as a minimally invasive approach. This technology primarily uses the da Vinci surgical system (Intuitive Surgical, Sunnyvale, CA, USA), although new platforms are in development. The first published reports on RATS were from the early 2000s, and since that time the technology has been rapidly adopted.[14–16] The popularity of a RATS approach is partly explained by the shorter learning curve necessary to obtain competency and mastery of the technique. As opposed to VATS lobectomy in which an estimated 50 cases are required for competency, the learning curve for RATS is an estimated 22 lobectomies.[17–19] The advantages of robotics are founded in the platform using a hybrid of both open and VATS approaches: instruments that move and perform functions similar to a human hand through an open incision, however, miniaturized and through keyhole incisions to achieve the patient-specific benefits of VATS.

Direct comparison of RATS and VATS has demonstrated minimal differences. In multiple studies, perioperative morbidity is equivalent.[20–22] There is a slight advantage to RATS in nodal harvest, but so far this has not been associated with an increase in nodal upstaging or survival.[23,24] RATS may be associated with increased cost, but this can be partially explained by the upfront costs associated with early adoption.[25,26] Although a minimally invasive approach is preferred over open thoracotomy, there is no clear advantage of one minimally invasive approach over the other (**Table 1**).

Table 1
Approaches to surgical resection of lung cancer

Approach	First Adoption	Advantages	Disadvantages
Thoracotomy	1930s	• Direct palpation of lung • Direct visualization of the lung surface	• Increased postoperative pain • Increased length of stay
VATS	1990s	• Reduced postoperative morbidity • Reduced length of stay • Digital palpation of most of the lung surface	• Visualization dependent on quality of thoracoscope • Longer learning curve • More difficult nodal dissection
RATS	2000s	• Reduced postoperative morbidity • Reduce length of stay • High-definition thoracoscope • Reduced learning curve	• No access for digital palpation • Lack of hepatic feedback • Increased cost

SURGERY IN THE SETTING OF NEOADJUVANT THERAPY

Chemoradiotherapy and more recently chemotherapy plus immunotherapy is the preferred treatment in patients who present with locally advanced, stage IIIa/IIIb disease or larger central node-negative tumors in which neoadjuvant therapy may improve resectability.[27–30] Compared with upfront surgery, operative resection after neoadjuvant has shown a clear benefit in this patient population.[31,32] Surgery after neoadjuvant treatment can be challenging due to treatment-related changes, which can make operative resection more difficult and increase the risk of bronchial stump breakdown. Despite this risk several studies have demonstrated the safety of surgery after immunotherapy.[33] Yang and colleagues[34] showed no difference in perioperative mortality or morbidity in a cohort of patients receiving chemotherapy as well as ipilimumab compared with historical controls. Likewise, Bott and colleagues[35] demonstrated the safety of neoadjuvant treatment with nivolumab followed by surgical resection. Such results served as the foundation for larger neoadjuvant trials, including Checkmate 816, in which combination neoadjuvant nivolumab plus chemotherapy was associated with longer event-free survival and higher rate of complete pathologic response compared with chemotherapy alone.[36] Although these trials cast a wide net regarding patients for inclusion, these results are more provocative for patients with locoregional disease and a greater than 1% expression of Programmed death-ligand 1 (PD-L1). Additional studies using larger cohorts and greater follow-up will be needed to determine the true benefit of immunotherapy in the neoadjuvant setting.

Equally important is the role of salvage surgery in patients with locally advanced disease that either recurs or demonstrates only a partial response to treatment. In these patients with locoregional failure, surgery can offer a potential benefit.[37] The benefits of salvage surgery vary widely in the literature with a 3-year survival ranging from 20% to 78%.[38,39] Complication rates in patients undergoing salvage surgery tend to be higher, and there is a frequent need for pneumonectomy or bilobectomy.[40] In a meta-analysis comparing long-term survival there is a clear advantage to surgical resection in patients when a pneumonectomy can be avoided.[41] There is also significant heterogeneity with patients who have early recurrence and death as well as long-term survivors (>5 years).[42] Predicting which patients may benefit from salvage surgery remains an area of continued investigation.

SEGMENTECTOMY AND SUBLOBAR RESECTION FOR EARLY-STAGE NON–SMALL CELL LUNG CANCER

Surgical resection for NSCLC can be accomplished through 3 methods: lobectomy, segmentectomy, or wedge resection. Lobectomy mandates the formal resection of the associated bronchus, pulmonary artery, and pulmonary vein to the specified lobe. Segmentectomy mandates the resection of the segmental bronchus and at least 1 of the associated vascular structures (typically the segmental pulmonary artery).[43] In both cases the associated nodal basin is taken with the specimen. In contrast, a wedge resection simply requires the resection of tumor and associated parenchyma without regard to the underlying anatomic structures. The nature of this operation restricts the opportunity to fully resect local lymph nodes and draining lymphatic pathways in a similar fashion to anatomic resection.

In 1995 the North American Lung Cancer Study Group published the results of a randomized clinical trial comparing lobectomy to limited resection (wedge resection or segmentectomy) for early-stage NSCLC (T1N0). The results of that trial demonstrated an unequivocal disadvantage to limited resection, with a 30% increase in death rate and a 50% increase in observed death with cancer rate.[44] However, accrual for the study occurred between 1982 and 1988 before the widespread adoption of computed tomography (CT) and PET. In addition, a significant proportion of patients in the sublobar resection group were treated with wedge resection.

Given the significant improvements in staging that have occurred with the rise of CT and PET-CT, 2 additional trials were performed to reassess the benefits of limited resection. The first, JCOG0802, compared lobectomy with segmentectomy for small ($\leq$2 cm) clinical stage Ia tumors with a consolidation-to-tumor ratio (CTR) greater than 0.5.[45] The results showed a modest but statistically significant 5-year survival advantage to segmentectomy over lobectomy (94.3% vs 91.1%). Similarly, the CALGB/Alliance 140503 demonstrated noninferiority of sublobar (wedge or segmentectomy) resection in node-negative NSCLC less than 2 cm in diameter.[46] Although the impact of these recently reported studies remains uncertain, there is evidence supporting the use of anatomic segmentectomy in carefully selected small early-stage tumors with slow growth kinetics and low risk of nodal spread.

SURGICAL MANAGEMENT OF GROUND-GLASS OPACITIES

As a result of improvement and widespread adoption of CT scans, small subsolid nodules are commonly encountered.[47] Unlike sold nodules, ground-glass opacities (GGOs) are defined as hazy lung opacities with preservation of bronchial and vascular markings.[48,49] In the setting of pneumonia, interstitial lung disease, or other inflammation they can represent benign disease. However, persistent or growing GGOs, especially those that develop a solid component, may represent an early-stage adenocarcinoma.

Determining the threshold for intervention for GGOs is an ongoing challenge to the field. In up to 30% of individuals, GGOs are multifocal and overly aggressive intervention at one site (eg, lobectomy) can result in unnecessary morbidity or limited treatment options for additional sites.[50] Conversely, these tumors can eventually metastasize to lymph nodes and other organs and if surgery is delayed the opportunity for cure may be lost. Fortunately, 5-year survival is greater than 90% in most series, and for this reason the threshold for intervention has gradually increased over the past 2 decades.[51] Features on serial imaging warranting surgical intervention include maximal size greater than 3 cm, new solid area or growth of prior solid area by greater

than or equal to 2 mm on mediastinal windows, or growth by greater than or equal to 25% in a single year (total or solid area).[52] Likewise, the extent of resection for GGOs has gradually decreased. Most recently, the Japan Clinical Oncology Group and the West Japan Oncology Group demonstrated a 5-year relapse-free survival of 99.7% for peripheral GGOs with a CTR less than 0.25 treated with wide wedge resection or segmentectomy.[53] Based on these results sublobar resection seems to be efficacious along with systematic sampling of N1 and N2 nodes for this particular subgroup.[47]

Perhaps the greatest challenge for the thoracic surgeon in the operating room is the difficulty encountered in palpating these lesions. Unlike solid nodules, which can readily be identified, GGOs can often elude digital palpation.[54] In a RATS approach this is even more challenging because only the gentle brushing of the robotic instruments provides clues to the exact location of the GGO. For this reason fiducial markers or injectable agents are often placed by interventional radiology before surgery.[55,56] These agents include radiotracers, metal clips, and lipiodol. These agents can be used in combination with a thoracotomy, VATS, or RATS approach and are associated with 95% to 98% success rate in most series.[57–62]

NAVIGATIONAL BRONCHOSCOPY

The evolution of robotics in surgical practice also includes opportunities for nodule localization and biopsy. Although initially difficult to use and only a small improvement from traditional bronchoscopic options such as endobronchial ultrasonography,[63] the newest generation of robotic navigation platforms allow for access to more peripheral targets or nodules at challenging angles to the airway. In this format, the camera is mounted to a robotic arm, the control and movement of a robotic bronchoscope is precise and robotically driven, and angles for biopsy can be achieved without deflection in the airway to improve diagnostic yield. In a recently reported multicenter study including more than 50 patients enrolled from 5 centers, the diagnostic yield was greater than 90%.[64] This is an operator-dependent technology and best performed at centers of excellence with expertise and volume, which are both likely associated with successful sampling. Future iterations of robotic navigation harmonized with ablative technologies could have therapeutic applications for subgroups of high-risk patients or nodules not amenable to radiation or peripheral ablation.

SUMMARY

Thoracic surgery has made major strides in the past 3 decades. The advent of minimally invasive techniques has allowed for a significant reduction in perioperative complications and postoperative pain. Going forward, the field will be challenged to integrate neoadjuvant treatment while maintaining these hard-fought improvements in perioperative morbidity. Equally important, disparities in treatment need to be addressed. Despite clear advantages to minimal invasive techniques, open thoracotomy is still performed in more than 40% of patients with stage I NSCLC.[65] As in many other areas of medicine, poorer patients and those living in rural areas tend to have reduced access to optimal care.[66] For the full advantages of recent advancements to be realized equity of care needs to become a priority.

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AUTHOR CONTRIBUTIONS

B.V. Udelsman: conception, analysis, interpretation of data, and drafting of article. J.D. Blasberg: conception, analysis, interpretation of data, and drafting of article.

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