

# Surgery for Non Small Cell Lung Cancer - A Systematic Review

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**Abstract:** *The management strategy for the treatment of non-small-cell lung cancer (NSCLC) has been transformed by our improved understanding of the cancer biology and concomitant development of novel systemic therapies. Complete surgical resection of NSCLC continues to offer the best chance for cure or local and regional disease control and with improvements in minimally invasive techniques and enhanced recovery, the morbidity associated with surgical resection has been reduced. Patient-centered multi-disciplinary discussions that consider surgical therapy are associated with improved outcomes. Provided with promising novel therapeutic modalities including immune checkpoint inhibitors with or without chemotherapy, stereotactic radiotherapy, and targeted systemic therapies, indications for surgery continue to evolve and have expanded to include selected patients with advanced and metastatic disease.*

**Keywords:** non-small-cell lung cancer; lobectomy; pneumonectomy; sublobar resection; surgery;

## 1. Introduction

### Principles of Surgical Therapy for Lung Cancer

The aims of surgical therapy for NSCLC are to perform a safe and effective operation in order to achieve complete resection with negative margins and adequate clearance of lymph node basins that are at risk or involved and to return a patient to a functional state to either undergo additional therapy or return to his or her pre-operative activities. This overarching principle incorporates a patient-centered approach, with critical and intricate patient selection, leading to therapeutic options that optimize oncologic benefit and minimize risks of complications while considering goals of care set by the patient. Pulmonary function tests and predicted post-operative values are used to identify the ability of a patient to undergo resection safely and are combined with cardiovascular status and additional deleterious comorbidities that may represent contraindications (1). The choice of procedure and approach comes with the decision to operate. There are trials investigating the outcomes from sublobar resections compared to lobectomies or pneumonectomies, providing data specifically regarding oncological outcomes relative to the size of the tumor and nodal status, setting the lobectomy as the standard and most common oncologic resection (2) while retrospective work highlights that sublobar resections can be oncologically sufficient in a highly selected cohort (3). Peri-operative mortality and morbidity continue to improve with the propagation of enhanced recovery after thoracic surgery (ERATS) pathways. The use of post-operative early ambulation, multimodal opioid-sparing analgesia and reduction of surgical stress has led to improved post-operative outcomes including pain control, decreased length of stay, and decreased pulmonary and cardiac morbidity during open operations (4). Most importantly, implementation of the ERATS pathways has facilitated the delivery of adjuvant chemotherapy. By promoting a more rapid return to baseline function, ERATS has enabled patients to resume systemic therapy more quickly and facilitates the completion of full four cycles of

therapy. These concepts are important especially with the approval of osimertinib and atezolizumab (5) as adjuvants to surgery and chemotherapy in stage IB-IIIa NSCLC. Mediastinal lymph node sampling during index operation compared to complete dissection also remains a source of discussion. Comprehensive nodal assessment is integral to the principles of surgical therapy for lung cancer. Clearance of at-risk lymph nodes is a cornerstone of optimizing survival benefit and depends on mediastinal nodal disease status. While the evidence remains equivocal, a large randomized controlled trial (ACOSOG Z0030) highlighted that in the event that systematic mediastinal and hilar lymph node sampling is negative, completion of mediastinal lymph node dissection did not improve survival in patients with N0 or nonhilar N1, T1, or T2 NSCLC (6). Whether nodal dissection of clinically positive mediastinal lymph nodes improves survival remains unanswered; however, authors recommend complete ipsilateral mediastinal nodal dissection in this setting to enhance regional disease control.

## 2. Material and Methods

A search of electronic databases including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) was undertaken using the keywords "lung cancer, non-small cell lung cancer. Systematic reviews, randomized clinical trials, retrospective cohort and cross-sectional studies written in English over the period 1995 – 2022 were evaluated for inclusion. Guideline recommendations from the National Cancer Care Network were also included and referenced.

## 3. Results and Discussion

### Staging and Classification of Lung Cancer

The TNM (tumor, node, metastasis) staging schema, originating in the 1970s, has continued to evolve along with our knowledge of lung cancer. The current eighth edition of the American Joint Committee on Cancer's TNM lung cancer classification was introduced in 2017 (7). Stage 0

encompasses all NSCLCs with a tumor that has not invaded the submucosal layer. Stage Ia relates to node-negative tumors that are less than 3 cm, while stage Ib relates to tumors that measure up to 4 cm. Stage II NSCLC relates to tumors that are less than 5 cm with nodal spread or less than 7 cm without nodal spread. Stage III comprises larger tumors and is divided into surgically resectable or unresectable. Stage IV NSCLC is routinely unresectable and has spread distally with metastases (8). Treatment is often determined by the stage of disease at the time of diagnosis, with surgery considered an appropriate adjunct to multimodal therapy for stages I–III and oligometastatic disease.

### Surgical Indication by Stage

#### Stage Ia

Patient-centered treatment is the cornerstone of lung cancer surgical management, and medically operable patients with stage 1 lung cancer should be considered for curative-intent pulmonary resection. Numerous studies have concluded that surgical management of this patient population is the standard of care and provides superior outcomes and locoregional control compared to other modalities, in part due to the benefits associated with mediastinal lymph node dissection both for further diagnostic and curative purposes (9). Following the decision to operate on this patient population, the extent of the procedure can be a source of discussion. Multiple investigations have shown that in the case of tumors less than 2 cm in size, a segmentectomy can lead to oncologically sufficient outcomes and lung-cancerspecific survival without any difference in perioperative mortality or morbidity. As such, segmentectomy should be strongly considered in this population as outcomes are comparable to lobectomy. For tumors 2.1–3 cm-in size, lobectomy remains the standard of care (10) while segmentectomy can be considered as a recent investigation established similarity in oncologic and overall outcomes between segmentectomy and lobectomy for patients without nodal disease. A large phase 3 clinical trial (NCT00499330) due to be completed in 2024 will provide further evidence regarding the optimal surgical approach (lobectomy versus segmentectomy or wedge resection) for management of stage 1 lung cancer (11). The decision whether to perform a resection with minimally invasive techniques such as video-assisted thoracoscopic surgery (VATS), robotic-assisted thoracoscopic surgery (RATS), or in an open manner remains associated with patient-centered factors considering that both open or minimally invasive approaches show similar oncologic outcomes, with VATS being associated with longer operative time but both minimally invasive approaches leading to shorter hospital stays (12). The best alternative to surgical resection for stage I NSCLC is stereotactic ablative radiotherapy (SABR). Previous work subjected to ongoing discussion concluded that SABR showed non-inferiority to minimally invasive lobectomy with mediastinal lymph node dissection with similar 3-year overall survival between propensity-matched cohorts following multidisciplinary discussion and patient preference; however, these trials were slow to accrue and performed their analysis early (13).

#### Stage Ib

Patients with stage 1b disease will have tumors larger than 3 cm but smaller than 4 cm. These patients should undergo primary tumor resection followed by tumor profiling, specifically to investigate mutations including those related to the epidermal growth factor receptor (EGFR) (14), which then permits consideration for targeted therapy. Patients with tumors between 3 and 4 cm will also benefit from a primary operation, the extent of which deserves deliberation. The options consist again of sublobar or lobar resection. A large retrospective study has shown that patients undergoing lobectomies for tumors between 2 and 5 cm were more likely to have >10 lymph nodes removed which was associated with improved survival and cancer-specific mortality (15). Despite slightly larger tumors than those seen in stage 1a, this cohort continues to benefit from minimally invasive resections and its associated decreased morbidity compared to open approaches (16). Therapy utilizing tyrosine kinase inhibitors, specifically osimertinib, has shown superiority in patients with EGFR mutations, with prolonged disease-free survival, a benefit that persisted on subgroup analysis of patients with stage 1b disease. Considering the use of neoadjuvant chemotherapy, despite being associated with down staging in some patients, was not associated with having any effect on oncologic surgical outcomes or overall survival in patients with stage 1b NSCLC (17). It is debated whether patients with stage 1b disease will benefit from adjuvant chemotherapy according to revised analyses from the Cancer and Leukemia Group B (CALGB) 9633 Trial indicating only a trend toward survival benefit in select patients with stage IB disease (tumors  $\geq$ 4 cm in size) (18).

#### Stage II

Patients suffering from stage 2 lung cancer will benefit from surgical resection as well, with aims of cure and locoregional control. However, patients with stage II also need systemic therapy, and this stage meets inclusion criteria for all ongoing neoadjuvant and adjuvant clinical trials as well as the standard of care adjuvant chemotherapy plus targeted or immunotherapy. Special attention must be placed on multidisciplinary discussions and multimodal protocols as the evidence for stage 2 disease is scarce due to a paucity of patients diagnosed at this stage. There are clinical trials investigating the optimal strategy to manage these patients using the currently available modalities, bolstering that the use of adjuvant chemotherapy has shown benefits in this cohort (19) even in patients with completely resected tumors, while the use of post-operative radiotherapy (PORT) is associated with benefits in patients with incompletely resected stage 2 disease and decreased mediastinal relapse without affecting disease-free survival (DFS) in patients with N2 involvement and complete resection (20). Given the paucity of evidence surrounding the optimal extent of surgical resection, patient-centered decisions must be made. In a recent retrospective study that included over 60 patients with stage 2 lung cancer within a larger cohort of patients with stage 1 lung cancer, early results show that long-term outcomes were similar between sublobar resections and lobectomies (21); however, these results merit further conscientious investigation following full publication of their results. In this patient population, mediastinal lymph node dissection must occur and is associated with a benefit

in locoregional disease control when compared to mediastinal lymph node sampling only, with improved 5-year survival and without any added post-operative mortality (22). Authors favor lobectomy with mediastinal node dissection in this setting.

### Stage III

Stage 3 has been the most controversial lung cancer stage due to its heterogeneity and multiple treatment options yet historically overall poor outcomes. Controversies relate to resectability, single or multiple or “bulky” N2 nodal disease status, contralateral or N3 mediastinal nodal disease, types of neoadjuvant therapy, and the appropriate extent of surgical resection, if any, in this setting. Immunotherapy has been redefining treatment paradigms in this setting and after many years also improving survival. Patients with stage III disease benefit from multidisciplinary evaluation with the first decisions being whether the disease is resectable or unresectable. While resectability may be assessed differently by different surgeons, we generally consider patients with stage III NSCLC for operative management if disease control can be achieved via lobectomy and mediastinal node dissection. With the effectiveness of current adjuvant therapies, we do not consider multi-station N2 disease a contraindication. Pneumonectomy should receive individual consideration, especially with N2 disease although N0-1 status is considered for resection. N3 nodal disease remains a contraindication for surgery.

### Stage III Resectable Disease

Despite the results originating from a large phase III randomized clinical trial conducted by Albain et al., which showed an insignificant survival benefit associated with resection compared to primary chemo-radiation when patients required a larger resection such as a pneumonectomy (23), lobectomy, coupled with meticulous perioperative care, can provide meaningful outcomes in stage III disease. In highly selected patients, surgical resection plays a significant role in a multimodal therapeutic strategy and is associated with improved overall survival (24) and locoregional recurrence benefit (25). While selection bias can be a limitation in work published regarding stage III disease, careful designation of patients who will benefit from surgical resection should originate from multidisciplinary meetings and can therefore mirror the inclusion criteria reported in these highly selective clinical trials.

Historically, for patients with stage III disease, with involvement of the ipsilateral mediastinal and/or the subcarinal lymph nodes (N2 disease), whether single-station or multi-station, oncologic benefit was obtained via induction chemotherapy or concurrent neoadjuvant chemoradiotherapy. While it remains the case that patients in this group, with N2 disease, are candidates for induction therapy (26), neoadjuvant chemoradiation can be associated with significant surgical mortality and morbidity (27), and the decision regarding neoadjuvant modality should remain a source of discussion given equivalence in recurrence patterns between neoadjuvant chemoradiation versus neoadjuvant chemotherapy (28).

Patients who require aggressive resections including pneumonectomies should undergo a closely established patient-oriented multidisciplinary discussion regarding goals of care and optimal treatment strategy based on clinicopathologic characteristics. The optimal treatment strategy for this complex group of patients continues to evolve as clinical trials culminate and provide further evidence regarding multimodal approaches such as the INCREASE trial investigating the role of neoadjuvant therapy in resectable and borderline resectable stage III lung cancer patients with tumors larger than 5 cm in size (29). Immunotherapy-containing regimens, with or without chemotherapy, as well as targeted therapies tested or under clinical evaluation in patients with resectable stage III disease as well have been discussed above.

### Stage III Unresectable Disease

Patients with stage III disease that is characterized as unresectable, comprising approximately 20% of all cases of lung cancer in the United States (30), will benefit from multimodal therapy, whether for life-prolonging intent, for palliation, or in hopes of converting resectability status. Historically, the standard of care for this group of patients has involved chemoradiotherapy (31) without induction chemotherapy; however, this continues to be associated with poor overall survival (32). Multiple large trials have investigated the use of immunotherapy or proton therapy in this cohort. The PACIFIC trial (phase 3), investigating the consolidative use of a PD-L1 inhibitor (durvalumab) for up to 12 months, in patients with stable unresectable stage III disease following chemoradiotherapy, irrespective of PD-L1 expression levels, showed that its use was associated with a prolonged progression-free survival, decreased rate of distant metastasis, and significantly increased time to distant metastasis (23.2 months vs. 14.6 months in placebo) (33). These therapeutic advantages were maintained at a 4-year landmark analysis, with median overall survival in the durvalumab group being 47.5 months compared to 29.1 months in the placebo group (overall survival hazard ratio (HR) = 0.71, progression-free survival (PFS) HR = 0.55) (34).

The benefits of immunotherapy following primary chemoradiation are tenable and resulted in increased consultations for salvage surgical resection in this patient cohort following the development of local or regional recurrence sometimes months to years after the index therapy. While maintenance checkpoint inhibition provides improved outcomes, these sites of recurrence will often have developed significant therapy-related inflammation and fibrosis (35). Such salvage surgical cases require significant skills and judgment for safe, margin negative resections in order to maintain adequate post-operative mortality and morbidity (36). The landscape of management of unresectable stage III disease is very quickly evolving, and close attention must be paid to guidelines that encompass multimodality and multidisciplinary management of this heterogeneous patient population. Additionally, there are several clinical trials testing or that have evaluated immunotherapy with radiation therapy for patients with unresectable stage III disease, which are beyond the scope of this review focused on resectable disease.



**Stage IV**

For patients with stage IV disease, the presence or absence of select actionable genomic alterations and the PD-L1 tumor expression status guide the use of standard of care targeted therapies, immunotherapy and chemotherapy plus immunotherapy (with or without an antiangiogenic agent) (37). Curative-intent surgery has not been offered for stage IV disease; however, locoregional disease control may have its benefits, especially in the oligometastatic setting. Surgical management for this particular cohort has been shown to provide better overall survival and improvement in disease-free intervals (38). The extent of resection offered to this patient population is usually limited to lobectomies with mediastinal lymph node resection (39). A particular principle to consider for this patient population is that while their initial disease stage is metastatic, following responses to therapy, the overall cancer burden may decrease sufficiently to allow for complete visible primary and metastatic disease consolidation and control.

**4. Conclusions**

The field relating to lung cancer management is one of the most exciting there is in surgical oncology, with an incredibly motivated multidisciplinary team relentlessly working to pioneer individualized patient-centered care and tailor current therapies to maximize clinical benefit.

Careful patient selection and timing of multi-modality therapy to permit the optimization of therapeutic benefit must be pursued. While chemotherapy and radiotherapy continue to have a role in the management of lung cancer, surgical therapy remains an essential component of lung cancer treatment in early, locally and regionally advanced, as well as in selected, cases of metastatic disease.

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