Surgical Management of T₃ and T₄ Lung Cancer

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Abstract
Locally advanced lung cancer (T₃ or T₄) has a significantly worse prognosis than lower stage disease. However, this diagnosis is usually made radiologically, and experienced thoracic surgeons are familiar with the low radiologic to pathologic correlation in tumors that abut the great vessels, mediastinum, or chest wall. Commonly these tumors do not directly invade adjacent structures and are, in fact, T₁ or T₂ tumors that are resectable through standard techniques. Where there is no clearly evident invasion of unresectable structures, the patient should be given the benefit of the doubt and considered at a lower (resectable) stage until proven otherwise. The curability of T₃ tumors varies according to the involved site. A T₃N₀ tumor involving the chest wall provides the most favorable prognosis among the resected T₃ lesions, with a 5-year survival of >50% in lymph node–negative patients if resection is complete. Palliative incomplete resections of T₄ disease, in which tumor has invaded mediastinal structures, have not shown any survival benefit and are associated with very high morbidity and mortality. However, patients with limited invasion of the carina, left atrium, superior vena cava, or pulmonary artery may be able to be completely resected despite their T₄ classification. Surgical resection remains an important part of the therapy for patients with locally advanced lung cancer. Modern techniques of chest wall resection and reconstruction and bronchoplastic procedures allow complete resection of locally advanced tumors with favorable 5-year survival rates and low morbidity and mortality.

Locally advanced lung cancer, where the primary tumor is close to the carina, invading the chest wall or diaphragm (T₁), or invading adjacent structures or organs (T₄), has a significantly worse prognosis than lower stage disease. T₃ lung cancers are those of any size with direct extension into the chest wall, diaphragm, mediastinal pleura, or are within 2 cm of the carina, without involving the heart, great vessels, trachea, esophagus, or vertebral body. T₄ lung cancers are defined by invasion of the heart, great vessels, trachea, esophagus, vertebral body, carina, presence of malignant pleural or pericardial effusion, or with a satellite tumor nodule in the primary tumor lobe. Involvement of adjacent structures confers a T₃ status when these structures are resectable (chest wall, superior sulcus, diaphragm, pericardium), whereas T₄ tumors have typically been considered unresectable by definition.

When surgical treatment results in total removal of the primary tumor and involved lymph nodes, there is still a reasonable chance for cure, even in these locally advanced cancers. Total excision can usually be done in T₃ tumors, and reflecting this, the current staging system has classified these as stage IIB in the absence of lymph node involvement. However, most T₄ disease is truly unresectable and is the reason for its continued classification as stage IIIB. Nonetheless, within T₃ and T₄ disease is a wide spectrum of biological behavior, represented by the degree of lymph node involvement, which itself is a strong surrogate for distant metastatic disease. Isolated T₃N₀ disease has rarely been evaluated as to its biological behavior and the outcome of aggressive surgical resection. Most studies combine all stage IIIB patients without distinguishing between T₄N₀ to N₁ tumors and the larger group of patients with T₁ to T₄N₃ and T₄N₂ disease. T₄N₀ tumors are unlikely to be biologically the same as T₁ to T₄N₂ tumors and, by definition, are tumors with less propensity to metastasize. Certainly, T₃N₀ disease has a negligible opportunity for surgical cure, but similar to T₄N₀, the subset of T₄N₀ patients with tumors that can be completely resected by current surgical techniques might have a legitimate possibility of prolonged survival.

Future biological staging may be able to provide a more accurate prognosis after complete resection for T₄N₀ tumors, and outcomes may further improve due to newer induction therapies and novel chemotherapeutics, e.g., cyclooxygenase-2 inhibitors and vascular endothelial growth factor inhibitors (1). In the future, lung cancer staging revisions may also redefine certain subsets of T₄N₀ lung cancers, encouraging consideration of surgical resection where previously the label of stage IIIB cancer has discouraged even a consultation with a thoracic surgeon.
Staging $T_3$ and $T_4$ Lung Cancer

Staging has the important role of trying to stratify groups of patients with similar prognoses who would benefit from similar therapeutic strategies. As important as this role is, it is susceptible to limitations of imaging, and staging definitions may lag behind advances in surgery, radiation, or chemotherapy that change the outcome in certain subgroups of patients. In lung cancer, the goals of staging are 2-fold: first, to avoid overstaging and the tragedy of palliative rather than curative intent therapy. This cannot be emphasized enough, particularly in considering that patients with clinical $T_3/T_4$ tumors are frequently directed away from surgical consideration without defining resectability and nodal status. The second goal of staging is to avoid understaging that may result in a nontherapeutic thoracotomy, with unnecessary morbidity, and the delay of appropriate chemotherapy or radiation. Although avoidance of understaging is very important, the consequences of understaging are much less severe than the consequences of overstaging, where the incorrect allocation to a more advanced stage produces the self-fulfilling result of patient death in the absence of curative intent therapy. Because of this imbalance, when uncertainty exists in clinical staging, the default position for treatment planning should give the benefit of the doubt to the patient, and assign the lower clinical stage until further imaging or surgical staging proves otherwise.

The initial diagnosis of locally advanced lung cancer is made radiologically, although the data indicate that radiologic specificity and sensitivity for determining involvement of structures adjacent to lung cancers are poor in the absence of clear-cut tumor infiltration. Cangemi et al. (2) report an accuracy of 91% and 27% for the staging of $T_1$ and $T_4$ lung cancers, respectively, with the use of chest computerized tomography (CT). Gdeedo et al. (3) report that overall, CT staging for $T_3$ or $T_4$ lung cancers was correct only 50% of the time. Comparisons of clinical and pathologic staging generally show that clinical staging underestimates the true pathologic stage. However, this is largely due to a lack of sensitivity in detecting occult mediastinal nodal and distant metastatic disease. The accuracy of staging is certainly improved by positron emission tomography (PET), with increased detection of previously unrecognized nodal or metastatic disease, and is further enhanced by routine techniques of surgical staging like mediastinoscopy (4). In contrast, T-staging is more commonly clinically overstaged than understaged. In a recent study examining this aspect specifically, Cetinkaya et al. (5) found that $T_4$ tumors were overstaged 26% of the time, compared with 12% understaging (and correct only 62% of the time). Even more dramatic was the incidence of overstaging of clinical $T_4$ tumors in 38% of cases, with the clinical implication two out of five potentially curable patients would not have been considered for surgical resection. This limitation of CT may be mitigated somewhat in specific circumstances by the utilization of magnetic resonance imaging, echocardiography, or transesophageal ultrasound, but there continue to be many patients with indeterminate findings. Experienced surgeons are familiar with the low radiologic to pathologic correlation in tumors that abut the great vessels, mediastinum, or chest wall. Commonly these tumors do not directly invade adjacent structures and are, in fact, $T_1$ or $T_2$ tumors that are resectable through standard techniques. Except in cases of clear-cut invasion of unresectable structures, the patient should be considered at a lower (resectable) stage.

**Patient Selection**

Whenever a surgical resection is being considered for patients with a potentially higher stage lung cancer, patient selection is paramount. Clinical $T_3$ disease is not a contraindication for surgery because the patient may have lower stage disease, with standard potential for resection, or have limited $T_4$ involvement that is amenable to complete resection by extended techniques. However, the benefit of surgery in these patients may be less, due to the increased probability of concomitant nodal or distant metastatic disease, compared with clinical $T_1$ to $T_2$ tumors. At the same time, the extent of surgery and its subsequent morbidity and mortality is greater, leading to a narrower risk/benefit ratio for surgical resection. Because the presence of mediastinal nodal disease is such a strong predictor of systemic failure, even with aggressive surgery, it is important to identify and exclude patients with $N_2$/$N_3$ nodes as carefully as possible. In all patients undergoing lung cancer staging, detection of metastatic disease is very important, but even more so in patients with locally advanced tumors who have a higher likelihood of distant disease and greater risk from surgical resection.

PET scan is a very useful adjunct to staging, both to exclude metastatic disease and to help identify and localize possible mediastinal nodal involvement. PET is not yet required staging for lung cancer in general, but probably should be done in all patients considered for extended surgical resections because of its benefit in refining clinical stage. Even with the combined accuracy of chest CT and PET, mediastinoscopy is mandatory to help confirm or exclude $N_2$ or $N_3$ nodal disease prior to surgical exploration particularly for $T_3$ and $T_4$ lung cancers.

Although PET imaging is a very good screening technology for detecting occult metastatic disease, it does not assess central nervous system involvement or skeletal metastatic disease outside of the PET field. PET does seem to be more sensitive for bony metastases than bone scanning, but PET protocols are frequently confined to the neck and trunk and could miss bony metastatic disease. In the absence of symptoms or signs, routine central nervous system imaging and bone scanning detect metastatic disease in only 6% and 10% of patients, respectively (6). Therefore, these modalities are not routinely used at our center for staging of asymptomatic patients with resectable disease. However, the yield of occult metastasis is probably higher in the subset of patients with $T_3/T_4$ tumors, and it is reasonable, but not mandatory, to add brain magnetic resonance and/or bone scan in the staging workup of these patients.

Patients undergoing consideration for extended surgical resection have increased risk of morbidity and mortality, and require a careful assessment of comorbid disease before undergoing surgery. Resection of the lateral chest wall for patients with $T_3$ disease has minimal added risks compared with lobectomy or pneumonectomy, and so only the standard contraindications to surgery apply and extra physiologic tests are not routinely necessary. However, the extended resections required for $T_4$ tumors do confer a significantly increased risk...
for these patients, and careful patient selection is paramount to minimize surgical morbidity and to offer a greater chance of prolonged cancer-free survival. These patients must have acceptable pulmonary and cardiac performance status with minimal comorbidities. Relative contraindications are age >70, diminished functional status, and cardiac or pulmonary limitations that substantially increase surgical risk. These operations are not well-tolerated by patients with marginal cardiopulmonary reserve, and additional testing may be appropriate in the preoperative assessment of these patients.

### Surgery for T3 Chest Wall and Superior Sulcus

Tumors with possible or probable chest wall or diaphragm involvement do not require any specialized imaging, and these patients can proceed directly to surgery after careful nodal and systemic staging. Superior sulcus tumors have a much higher propensity for invasion into unresectable structures due to the proximity of the brachial plexus, vertebral bodies, and subclavian vessels. Magnetic resonance imaging is helpful in these patients to refine the anatomy at the thoracic inlet and exclude the presence of any unresectable extension of tumor.

New surgical approaches have provided better technical resection for some tumors. Dartevelle et al. (7) have recently described anterior approaches to anterior superior sulcus tumors to provide direct access to the tumor underlying the subclavian vessels. Vascular resection and reconstruction can be done when need be for lung cancer, particularly superior sulcus tumors, with reasonable postoperative morbidity and mortality, while achieving the goal of complete resection (8). Vertebral body resections in certain circumstances can be done with reasonable postoperative mortality (9). Patients with Pancoast tumors are also the one subset of patients who clearly benefit from induction therapy. Historically, these patients have benefited from preoperative radiation followed by surgery, probably due to the improved ability to perform a complete surgical resection. More recently, this has been further refined, with the current recommendations for neoadjuvant chemoradiotherapy for T3 and T4 superior sulcus tumors, ultimately facilitating complete resection and prolonging survival (10, 11).

All T3 tumors are resectable, but the prognosis varies according to the involved site. A T3 tumor involving the chest wall provides the most favorable prognosis among the resected T3 lesions. If completely excised, T3 (chest wall) N0 lung cancers provide a 5-year survival in excess of 50%. This is diminished to ~30% to 35% for chest wall lesions involving the superior sulcus, which may be due to the additional difficulty in obtaining a complete surgical resection in these apical tumors (refs. 12–17; Table 1). The strongest determinants of 5-year survival, by far, are completeness of resection and nodal status. Surgeons undertaking these operations must be very experienced in order to accurately identify candidates for resection and not exclude patients with possibly resectable tumors due to inexperience or excessive conservatism. Likewise, experience in the specialized resections required is critical to assure a complete resection, because this offers the only opportunity for surgical cure. Occasional thoracic surgeons may be intimidated by the extended boundaries required for resection when including adjacent non–pulmonary structures, resulting in excessive caution and tragically incomplete resections that are nearly impossible to salvage with further surgery, chemotheraphy, or radiation.

### Mediastinal Invasion and Central Airway T3 and T4 Lung Cancers

The critical evaluation of the patient with an airway T3 tumor is bronchoscopy to determine the exact details of airway involvement, including proximal and distal extent of tumor, and the feasibility of complete resection with airway reconstruction as well as the extent of pulmonary resection. It is important that the bronchoscopy is done by the operating surgeon close to the time of the planned resection in order to accurately predict the extent of resection necessary. Mediastinoscopy will not only rule out N2 disease but will allow direct examination of the proximal extent of tumor outside of the airway, and can help distinguish T3 from T4 disease, determine resectability, and initiate mobilization of tissue planes that are essential for airway reconstruction. Mediastinoscopy must be done at the time of surgery and not at a different date. This is because postoperative paratracheal scarring may complicate bronchoplastic or tracheoplastic procedures. Mediastinoscopy does have its pitfall in these central lung cancers, however, which is a possible false-positive finding in cases where the central tumor is directly biopsied by the unsuspecting surgeon, but attributed to N2 nodal disease rather than to the primary tumor.

Patients with tumors in the mainstem bronchus within 2 cm of the carina are usually considered for resection by pneumonectomy. However, frequently, these patients’ tumors are considered “unresectable” because of the concerns regarding an adequate proximal margin or the adequacy of bronchial stump closure, or because the patient’s poor pulmonary function will not tolerate a pneumonectomy. However, sleeve lobectomy is possible in a majority of these patients and

### Table 1. T3 Chest wall resection

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Morbidity (%)</th>
<th>Mortality (%)</th>
<th>5-Year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watanabe et al. (12)</td>
<td>1991</td>
<td>42</td>
<td>NA</td>
<td>NA</td>
<td>43</td>
</tr>
<tr>
<td>Albertucci et al. (13)</td>
<td>1992</td>
<td>37</td>
<td>NA</td>
<td>NA</td>
<td>30</td>
</tr>
<tr>
<td>Pitz et al. (14)</td>
<td>1996</td>
<td>125</td>
<td>NA</td>
<td>8.3</td>
<td>29</td>
</tr>
<tr>
<td>Downey et al. (15)</td>
<td>1999</td>
<td>175</td>
<td>NA</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>Magdeleinat et al. (16)</td>
<td>2001</td>
<td>201</td>
<td>NA</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>Facciolo et al. (17)</td>
<td>2001</td>
<td>105</td>
<td>19</td>
<td>0</td>
<td>61</td>
</tr>
</tbody>
</table>
However, patients with limited T4 airway involvement of the superior vena cava, aorta, or left atrium may allow resection, most authorities consider invasion of the superior vena cava, aorta, or left atrium to be a contraindication to resection, although occasional bypass as a contraindication to resection, although occasional procedures have been performed. Systemic arterial (aorta) and esophageal invasion of T4 lung cancer carry the poorest long-term outcome. Although limited T4 involvement of the superior vena cava, intrapericardial pulmonary artery, phrenic nerve, or left atrium may allow resection, most authorities consider invasion of the esophagus, vertebral body, or great vessels as contraindications to surgery. Systemic arterial (aorta) and esophageal invasion of T4 lung cancer carry the poorest long-term outcome.

Limited local invasion of the intrapericardial pulmonary artery or left atrium can be resected completely with expected 5-year survival rates of ~20% to 30%. In general, if there is less than 1 to 1.5 cm of intrapericardial involvement of these structures, they can usually be resected with negative margins and a safe vascular closure. Most authorities have viewed the need for more complex reconstructions that require cardiopulmonary bypass as a contraindication to resection, although occasional procedures have been performed.

**Table 2. Sleeve lobectomy: 5-year survival by stage**

<table>
<thead>
<tr>
<th>Surgical series</th>
<th>I (%)</th>
<th>II (%)</th>
<th>III (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleeve lobectomy ($n = 1,915$)</td>
<td>63</td>
<td>37</td>
<td>21</td>
</tr>
<tr>
<td>Tedder et al. (18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeve lobectomy ($n = 104$)</td>
<td>79</td>
<td>55</td>
<td>30</td>
</tr>
<tr>
<td>Watanabe et al. (19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeve lobectomy ($n = 142$)</td>
<td>57</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>Mehran et al. (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonectomy ($n = 60$)</td>
<td>42</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Okada et al. (21)</td>
<td></td>
<td></td>
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</tbody>
</table>

This provides oncologically equivalent outcomes (18–21) to pneumonectomy with two distinct advantages (Table 2). First, sleeve lobectomy allows more proximal division of the mainstem bronchus, providing a better proximal margin without concerns regarding tension from a high pneumonectomy stump closure. This is due to the fact that the bronchial stump will be “closed” by performing an anastomosis with the distal bronchus, rather than requiring a longer stump for adequate closure without tension. Second, the preservation of distal pulmonary function provides the advantage of allowing complete surgical resection for patients who would have been deemed inoperable due to poor pulmonary function. This preservation of distal pulmonary function is useful even in patients who could tolerate pneumonectomy, due to the diminished operative morbidity and improved long-term functional outcomes of lobectomy compared with pneumonectomy (22). Occasionally, a concomitant pulmonary vascular sleeve resection may also be required. This should only be considered when the pulmonary artery is locally invaded by primary tumor rather than by lymph node metastasis.

Most patients with airway T4 disease also have invasion of other mediastinal structures that preclude surgical resection. However, patients with limited T4 airway involvement of the carina or distal trachea may also be considered for an extended surgical resection using bronchoplastic techniques. Resection of the distal trachea and carina, combined with a pneumonectomy, or occasionally lobectomy, can be reconstructed with a tracheal to mainstem bronchial anastomosis. Generally, this is only applicable if it is possible to achieve negative tumor margins with <4 cm of airway resection. These resections are fraught with significant morbidity and mortality, with an operative mortality of 10% to 15% and a long-term survival rate of approximately 20% to 40% (23–29). These operations should be limited to younger, good performance status patients who are better able to withstand an aggressive surgical approach (Table 3).

In the heterogeneous category of T3 mediastinal invasion, the most important detail (beyond elimination of nodal and systemic metastases) is the exclusion of T4 invasion, or at least T4 invasion beyond the scope of complete resection. The true T3 mediastinal tumors are those that involve the pericardium, mediastinal pleura, and pericardial fat, which may be very difficult to distinguish from T4 involvement of adjacent mediastinal organs or great vessels. Magnetic resonance imaging may help assess great vessel or vertebral body involvement, and transesophageal echocardiography may help assess left atrium, superior vena cava, and the midline great vessels. Minimally invasive staging with esophagoscopy, mediastinoscopy, anterior mediastinotomy (Chamberlain procedure), or thoracoscopy can help evaluate and answer specific questions.

The prognosis for patients with T3 mediastinal tumors is dependent on complete resection and is favorably influenced by single rather than multiple involved structures, with 5-year survival rates of 36% for node-negative patients (30). T4 mediastinal invasion by the primary tumor does not always contraindicate surgical resection. However, complete resection is paramount because “palliative” incomplete resections have not shown any survival benefit, provide questionable palliation, and are associated with a very high morbidity and mortality (31).

**Atrial, Aorta, Superior Vena Cava, and Vertebral Body Resection for T4 Tumors**

Although there are scattered reports of long-term survivors from extended resections of lung cancers involving the superior vena cava, aorta, esophagus, or vertebral body, there are fewer solid data to support these extended operations. There are no consistent data regarding these resections of T4 lung cancers. Although limited T4 involvement of the superior vena cava, intrapericardial pulmonary artery, phrenic nerve, or left atrium may allow resection, most authorities consider invasion of the esophagus, vertebral bodies, or great vessels as contraindications to surgery. Systemic arterial (aorta) and esophageal invasion of T4 lung cancer carry the poorest long-term outcome. Limited local invasion of the intrapericardial pulmonary artery or left atrium can be resected completely with expected 5-year survival rates of ~20% to 30%. In general, if there is less than 1 to 1.5 cm of intrapericardial involvement of these structures, they can usually be resected with negative margins and a safe vascular closure. Most authorities have viewed the need for more complex reconstructions that require cardiopulmonary bypass as a contraindication to resection, although occasional procedures have been performed.

**Table 3. Carinal resection**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>$n$</th>
<th>Morbidity (%)</th>
<th>Mortality (%)</th>
<th>5-Year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsujiya (23)</td>
<td>1997</td>
<td>20</td>
<td>40</td>
<td>15</td>
<td>59 (2-y)</td>
</tr>
<tr>
<td>Maeda et al. (24)</td>
<td>1993</td>
<td>42</td>
<td>-</td>
<td>15</td>
<td>NA</td>
</tr>
<tr>
<td>Roviaro et al. (25)</td>
<td>1994</td>
<td>49</td>
<td>10</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>Dartevelle and Macchiarini (26)</td>
<td>1996</td>
<td>60</td>
<td>11</td>
<td>7</td>
<td>40</td>
</tr>
<tr>
<td>Mitchell et al. (28)</td>
<td>1999</td>
<td>143</td>
<td>39</td>
<td>13</td>
<td>42</td>
</tr>
<tr>
<td>Porhanov et al. (29)</td>
<td>2002</td>
<td>231</td>
<td>35</td>
<td>18</td>
<td>25</td>
</tr>
</tbody>
</table>
patients may have anatomy where bypass may be a useful adjunct to resection. Vascular resection and reconstruction of the superior vena cava, aorta, and left atrium have been safely described with 5-year survival rates of 20%. Along with limited left atrial resection, superior vena cava resection is the most accepted extended vascular resection for T4 disease with an acceptably low mortality rate and 5-year survival rates ranging from 10% to 30% (refs. 32–36; Table 4). Combined pulmonary and aorta resection is described by Fukuse et al. (37) with 5-year survival rates of 31% (n = 15). Combined pulmonary and left atrial resection has been described most recently by Bobbio et al. (38) with 5-year survival rates of 10% (n = 23). Finally, T4 lung cancers invading the vertebral body can be resected with a 5-year survival rate of 15% (9). A multidisciplinary team is essential for these complex resections and reconstructions.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Morbidity (%)</th>
<th>Mortality (%)</th>
<th>5-Year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas et al.</td>
<td>1994</td>
<td>15</td>
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<td>7</td>
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<tr>
<td>Dartevelle et al.</td>
<td>1995</td>
<td>14</td>
<td>21</td>
<td>7</td>
<td>31</td>
</tr>
<tr>
<td>Spaggiari et al.</td>
<td>2000</td>
<td>25</td>
<td>36</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>Spaggiari et al.</td>
<td>2002</td>
<td>109</td>
<td>39</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Spaggiari et al.</td>
<td>2004</td>
<td>15</td>
<td>23</td>
<td>14</td>
<td>57 (3 y)</td>
</tr>
</tbody>
</table>

**Induction Therapy for T3 or T4 Tumors**

Induction therapy used for T3 or T4 tumors is an extension of stage IIIA (N2) preoperative chemoradiotherapy. The studies evaluating induction therapy for stage III lung cancer include a heterogeneous spectrum of locally advanced lung cancer. The majority of these are for N2 disease with very little data that can be extrapolated to T3/T4 disease without nodal metastases. The rationale for the consideration of induction therapy is 2-fold. First, the early treatment of presumed micrometastatic disease is an effort to improve median survival and disease-free survival by improving systemic control. Second, because these tumors are frequently marginally resectable, there is the hope that response in the primary tumor site may provide a better likelihood of achieving a complete resection for improved local control. A corollary of this is the possibility of accomplishing a less radical resection with less perioperative and long-term morbidity. Martinez-Monge et al. (39) showed the 4-year survival with induction therapy for T3 and T4 superior sulcus disease to be 56%. In two other studies examining induction therapy for superior sulcus tumors, Rusch et al. (10, 11) and Wright et al. (40), showed 5-year survival rates of (n = 111) 55% and (n = 49) 84%, respectively. Studies solely focusing on T3 and T4 without N1 or N2 disease are not available. Hainsworth et al. (41) found that induction therapy seemed to benefit those patients with locally advanced N0 to N1 disease; however, survival rates were not significantly better when compared with surgery alone, and induction therapy patients did have an increase in postoperative morbidity. The use of induction therapy is still controversial for locally advanced lung cancer except for those involving the superior sulcus. However, the potential for inhibition of micrometastatic disease should be considered in future studies, particularly with the influx of newer chemotherapeutics and antitumorigenic biological strategies.

**Conclusion**

Surgical resection remains an important option for patients with locally advanced lung cancer and can be done with acceptable postoperative morbidity and mortality. Preoperative imaging is often inaccurate in determining advanced T stage and should not be considered a contraindication to resection in the absence of consultation with an experienced thoracic surgical oncologist. The ability to accomplish a complete surgical resection and the lymph node status are the primary prognostic factors in considering extended resections for T3 or T4 tumors. It is important that a thoracic surgical oncologist be a primary component of the multimodality team making staging and treatment recommendations. Modern techniques of chest wall resection and reconstruction and bronchoplastic procedures allow complete resection of locally advanced tumors with favorable 5-year survival and low morbidity and mortality rates. Bronchoplastic procedures provide the advantage of allowing resection of central lung cancers, even in patients with poor pulmonary function, but have the added benefit of decreasing operative morbidity and mortality and improving long-term function and quality of life in patients who would have otherwise required a pneumonectomy or palliative chemoradiation. Several studies have also shown 5-year survival rates of 20% to 30% in specific subsets of patients with resection for limited involvement of the superior vena cava, left atrium, and pulmonary artery. Smaller series have reported limited success with resection of tumors with vertebral body involvement, usually in the setting of superior sulcus tumors. There is no sizable experience in resections of tumors involving the esophagus or systemic arteries, mostly consisting of case reports. The role of neoadjuvant or novel and conventional adjuvant therapies is unclear for these locally advanced tumors.

**Open Discussion**

Dr. Thomas Lynch: That point about getting the surgical go/no go decision before you start therapy is an important message to get out both to the thoracic surgeons and to the medical and radiation oncologists. Because you get into real trouble when you say, “Let’s give them some chemorads and see how they do.” They give them weekly carboplatin and paclitaxel at low doses and 45 Gy of radiation with the standard fractionation scheme. Then they wait 4 or 5 weeks and at that point they come to the
surgery. If you then decide that the person is not resectable, that patient hasn’t had the benefit of curative radiotherapy, say, 70 Gy given with conformal three-dimensional approaches.

Dr. Wood: I think that’s the worst possible management and it’s the most common. I see it all the time. “Let’s give them some chemoradiation and see how they do.” First of all, you’ve muddied the waters for consideration of definitive surgery because it becomes difficult at that stage for the surgeon to assess the patient’s true resectability. You don’t really know what is treatment effect versus tumor, both preoperatively and intraoperatively. Intraoperatively it’s difficult as well. And, as you said, if they’re not a surgical candidate, they have not had the appropriate definitive nonsurgical therapy.

Dr. Joan Schiller: So, if someone comes in with bulky, clinical stage N2 disease and we’re going to make this decision upfront, are we going to decide to give chemoradiation and then operate regardless of what happens?

Dr. Wood: I think bulky N2 disease is much more difficult to decide than select patients with T3, T4 disease. Bulky disease is probably best treated by definitive chemoradiotherapy.

Dr. Schiller: And part of the reason I have just raised the issue is because it affects clinical trial design. Our surgeons too operate regardless of what happens? If they’re not a surgical candidate, they have not had the benefit of curative radiotherapy, say, 70 Gy given with conformal three-dimensional approaches.

That’s a different definition than I would have of bulky. You’re talking about clinically evident N2 disease. N2 disease is resectable. The question is whether resection adds benefit.

Dr. Malcolm DeCamp: The benefit is just as much with the definitive chemoradiotherapy. I showed the data that surgery alone was just as good as chemoradiation based on the published literature. The intergroup trial already shows improved failure-free survival, albeit it’s only 3 months. We’ve got to see if that matures, but I think we can argue that both ways. When I think of bulky N2 disease, I’m talking about extracapsular disease going beyond the lymph nodes at multiple stations, not just one node positive.


Dr. Lynch: That was 30 patients per trial years and years ago.

Dr. Bogart: It was the basis of a change in treatment paradigm in the U.S., though.

Dr. David Gandara: Just for the purpose of discussion, for the new intergroup trial of chemoradiotherapy alone versus chemoradiation, bulky was defined as 3 cm or greater by consensus.

Dr. Lynch: Of the node. But, if within this group of lung cancer experts, we went around with a half hour of misunderstanding on what we meant by terminology, you see how challenging this situation is.

Dr. Glenwood Goss: What is the highest dose of radiation that your patients receive prior to surgery?

Dr. Wood: The highest is probably 70 Gy. However, when it is over 50 Gy and then you add time, the risks go up exponentially, particularly for these types of resections where you are doing airway anastomoses or complicated reconstructions. I am seeing patients who have had definitive chemoradiotherapy who then are sent for “salvage surgery,” which I think we ought to try and exclude as much as possible. If they otherwise seem appropriate for surgery, I’ll bring up a soft tissue flap that has been outside of the radiation field, but I think the risk is higher at that point.

Dr. Lynch: Just make sure you tell us when you do one of the intercostal muscle flaps so that when we do the CT afterwards we don’t look and say “Oh my gosh, they have recurrent disease!”

Dr. Wood: I put a flap on every bronchial stump and my radiologist knows it, but I get calls from outside radiologists to tell me about the new hilar mass on my recently resected cancer.


Clinical Cancer Research

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Costanzo A. DiPerna and Douglas E. Wood


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