Sublobar Versus Lobar Resection

Current Status

Chaitan K. Narsule, MD, Michael I. Ebright, MD, and Hiran C. Fernando, MBBS, FRCS

Abstract: Currently, lobectomy is the preferred treatment for early-stage, non-small cell lung cancer primarily because of the increased local recurrence rate that has been reported with sublobar resection. Sublobar resection is typically used for high-risk, but still operable, patients with lung cancer. Several recent studies have demonstrated comparable recurrence and survival rates between lobectomy and sublobar resection for small, stage I lung cancers. In particular, attention to technical details such as performing a segmentectomy or a wide wedge resection (rather than a simple wedge resection), or the addition of brachytherapy, can result in improved outcomes. Also, the potential for better preservation of pulmonary function with sublobar resection has fueled the debate arguing for sublobar resections even for patients who are considered to be “good risk” and able to tolerate a lobectomy. This article reviews the current status of sublobar resection for early-stage lung cancer, with particular attention to issues such as tumor size, type of sublobar resection, use of adjuvant brachytherapy, and preservation of pulmonary function.

Key Words: Sublobar resection, lobar resection, segmentectomy, wedge resection, brachytherapy

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In 1995, the Lung Cancer Study Group (LCSG) reported the only randomized trial comparing lobectomy and sublobar resection for the treatment of T1NO non-small cell lung cancer (NSCLC).1 In this study, a tripling of the local recurrence rate among patients who underwent sublobar resection was observed. Other nonrandomized studies compared patients undergoing sublobar resection to those who undergoing lobectomy and also demonstrated increased local recurrence in patients undergoing sublobar resection.2 For these reasons, lobectomy has remained the treatment of choice for stage I NSCLC, with sublobar resection reserved as a “compromise” operation for high-risk patients who are operative candidates but for whom an anatomic lobectomy is contraindicated.

Today, a number of factors are prompting the reevaluation of lobectomy as the optimal treatment for early-stage lung cancers that are peripheral in location and potentially amenable to a sublobar resection. These factors include the following:

(1) Tumor size: Patients with small tumors are less likely to have regional or distant metastases at the time of diagnosis, and have an overall better prognosis. Although the possibility of nodal disease decreases with smaller tumors, this is not zero, and even tumors that are 1 cm or less in diameter have been associated with up to a 7% incidence of occult nodal disease.3 Nevertheless, sublobar resection performed in conjunction with lymph node dissection may be a reasonable approach for very small peripheral tumors.

(2) Indolent behavior: With the increasing use of high-resolution computed tomography (CT), more indolent tumors such as bronchoalveolar carcinomas may be identified. Removing an entire lobe for such tumors may be overly aggressive.

(3) Pulmonary function: Larger lung resections will result in a loss of more pulmonary function and may restrict the ability to perform subsequent resections for recurrent tumors.

(4) Brachytherapy: Adjuvant intraoperative brachytherapy at the time of sublobar resection has been reported by a few centers.4–7 This effectively improves the surgical margin and results in lower local recurrence rates.

In this review, the debate of choosing between sublobar resection and lobectomy for small NSCLCs is explored, with particular attention to the factors mentioned above.

BRIEF HISTORY OF SUBLOBAR RESECTION

In the early half of the 20th century, pneumonectomy was considered the only appropriate treatment of primary lung cancer.8 However, because of the unacceptably high mortality rate associated with pneumonectomy (~40%) at the time, lobectomy evolved as the treatment of choice for resectable peripheral cancers.9 Although Churchill and Belsey10 first reported segmentectomy for the treatment of bronchiectasis in 1939, it was Jensik and colleagues11 who first described its use for lung cancer resection in 1973.

Subsequent studies reported the usefulness of segmentectomy as a compromise operation in selected, poor-risk patients.12–17 Notably, in 1985, Errett et al18 reported a 17-year experience in which 197 patients underwent wedge resection or lobectomy for bronchogenic carcinoma and demonstrated a 2-year survival of 72% versus 74%, as well as a 6-year survival of 69% versus 75%, a difference that was not statistically significant. Importantly, patients who underwent wedge resection had significantly impaired cardiopulmonary function and were not candidates for lobectomy.

Despite these early studies suggesting equivalency in survival between sublobar and lobar resection for lung cancer, the higher technical complexity of performing a segmentectomy, particularly in dissecting along the intersegmental plane which may increase the potential for a prolonged air leak, was of great concern to many surgeons. On the other hand, with a limited resection and further preservation of lung volume, perioperative morbidity and mortality can potentially be reduced, and opportunities for additional lung resection in the future could be maintained should the patient develop a recurrence or a second cancer.

In 1994, Warren and Faber19 reported a retrospective study of 169 patients with stage I NSCLC undergoing segmentectomy (66 patients) or lobectomy (103 patients) over an 8-year period. Both groups of patients were deemed able to tolerate a lobectomy. Of note, the locoregional recurrence rate for the segmentectomy group was significantly higher than for the lobectomy group (22.7% vs 4.9%; P < 0.05). It is interesting to see,
even in this early study, that there were similar 5-year survival rates in patients with tumors 2 cm or less in diameter (70% for lobectomy, 68% for segmentectomy; *P* = 0.24).

These studies inspired the LCSG study, reported in 1995, which involved 247 patients randomized into 2 treatment groups: limited resection (defined as either a wedge resection or segmentectomy) or lobectomy for T1N0 NSCLC. Although no significant difference existed in reference to perioperative morbidity or mortality, there was a significant threefold increase in the locoregional recurrence rate for the limited resection group.

There are several major criticisms of the 1995 LCSG report. The first is that a high percentage of patients in the sublobar resection group (32.8%) underwent a wedge resection. A wedge resection is not as effective as anatomic segmentectomy because immediate regional lymph nodes related to the tumor are not always removed, and the margin between the surgical staple line and tumor is more likely to be smaller. In contrast, lymph node sampling is usually superior with segmentectomy, allowing for better staging of the lung cancer. In other studies, poorer outcomes—in terms of survival—have been reported with wedge resections.²⁻²¹

In addition, patients with tumors up to 3 cm in diameter were included in the LCSG study. Tumor size is an important consideration when planning lung resection for early-stage NSCLC, as smaller tumors (≤2 cm in diameter) are less likely to be associated with regional or distant metastasis and are more likely to have equivalent outcomes with sublobar resection when compared with lobectomy.

A similar increase in local recurrence among patients undergoing sublobar resection was demonstrated in a prospective nonrandomized multi-institutional study by Landreneau and colleagues²⁷ in 1997, which compared wedge resection to lobectomy for T1N0 NSCLCs. Of note, 102 patients undergoing wedge resection (video-assisted thoracoscopic surgery [VATS], *n* = 60; open, *n* = 42) in this series had significantly impaired cardiopulmonary function, compared with the 117 patients treated with lobectomy. Although a higher local recurrence rate was seen in the overall wedge resection group compared with the lobectomy group (19% vs 9%; *P* = 0.07), the 5-year survival was not statistically different between these groups (*P* = 0.056) or between the VATS wedge resection and lobectomy groups (*P* = 0.889). The only significant difference in survival existed between the open wedge resection and lobectomy groups (*P* = 0.05). There were also no operative mortality, fewer complications, and a shorter length of stay for the wedge resection group.

### Current Thinking on Sublobar Resection

Over the last decade, many studies have emerged suggesting equivalency between sublobar and lobar resection for the treatment of peripheral, early-stage NSCLC. Many of these recent contributions emanate from investigators in Japan, where CT screening programs have been in place to detect lung cancer for over 10 years.²²⁻²⁴ Several of these groups have demonstrated comparable outcomes using sublobar resection as primary treatment for lung cancer, even in good-risk patients. Some of these studies are reviewed in Table 1. It is important to note that, despite the favorable outcomes seen among several Japanese reports, similar results may not necessarily be applicable to Western studies, owing to a higher incidence of more indolent lung cancers such as bronchoalveolar carcinoma, which is more likely to have improved survival at early stages of disease.²⁸

#### Small Stage I Tumors

As mentioned earlier, smaller tumors are less likely to exhibit nodal disease. In the past decade, several studies have demonstrated improved survival and decreased recurrence rates for patients with tumors 2 cm or less in diameter. In 2001, Okada et al²⁷ reported the outcomes of extended segmentectomy or lobectomy in patients treated for T1N0 tumors 2 cm or less and showed a 5-year survival rates of 87.1% in the segmentectomy group and 87.7% in the lobectomy group (*P* = 0.8008). The following year, Bando et al³⁰ reported on segmentectomy in 74 patients with T1N0 NSCLC. Overall 5-year survival was 82%, yet for tumors 2 cm or less, it was 92% as compared with 63% for the larger tumors (from 2.1 to 3 cm). In addition, the locoregional recurrence rate was 1.9% for those with tumors 2 cm or less, as compared with 33.3% for those with larger tumors (*P* < 0.01).

In 2003, Koike et al²⁷ reported a 9-year experience in which 159 patients were treated with lobectomy and 74 patients were treated with sublobar resection for T1N0M0 peripheral NSCLC 2 cm or less in diameter. Within the sublobar resection group, 60 patients underwent segmentectomy, and 14 underwent wedge resection. The 5-year survival was 89.1% for the sublobar resection group, compared with 90.1% for the lobectomy group. Moreover, 2 patients in each group developed local recurrences, translating to a local recurrence rate of 2.7% for the sublobar resection group and 1.3% for the lobectomy group.

Okada and colleagues³¹ reported a nonrandomized, multicenter, intention-to-treat study comparing 305 patients scheduled to undergo sublobar resection with 262 patients scheduled to undergo for lobectomy for T1N0M0 NSCLC of 2 cm or less in 2006. An overall 5-year survival of 89.6% was seen for the sublobar resection group, compared with 89.1% for the

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>No. Patients</th>
<th>5-y Survival</th>
<th>Local Recurrence*</th>
<th>Perioperative Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>Read et al²⁵⁺</td>
<td>113</td>
<td>84%</td>
<td>4.4%</td>
<td>3.5%</td>
</tr>
<tr>
<td>1994</td>
<td>Warren and Faber¹⁹⁺</td>
<td>66</td>
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<td>22.7%</td>
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</tr>
<tr>
<td>1995</td>
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<td>62</td>
<td>59%</td>
<td>22.6%</td>
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</tr>
<tr>
<td>1995</td>
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<td>17.2%</td>
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</tr>
<tr>
<td>1997</td>
<td>Landreneau et al²²⁺</td>
<td>102</td>
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</tr>
<tr>
<td>1997</td>
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<td>46</td>
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<td>2.2%</td>
<td>0%</td>
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<tr>
<td>2003</td>
<td>Koike et al²⁷⁺</td>
<td>74</td>
<td>89%</td>
<td>2.7%</td>
<td>0%</td>
</tr>
<tr>
<td>2004</td>
<td>Keenan et al²⁸⁺</td>
<td>54</td>
<td>62%</td>
<td>11.1%</td>
<td>5.6%</td>
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</table>

*Definitions of local recurrence are different from definitions used in SBRT/RFA literature.

†Stage IA.

NA indicates not available.

### Table 1. Survival, Local Recurrence, and Perioperative Mortality Rates in Patients Undergoing Sublobar Resection for Stage I NSCLC
lobectomy group ($P = 0.106$). Also, 5-year cancer-free survival was 85.9% for the sublobar resection group, compared with 83.4% for the lobectomy group ($P = 0.2778$).

Despite these impressive results from Japan, not all studies have demonstrated similar rates of survival. In 2002, Miller et al. reported results of a retrospective study involving 100 patients who underwent surgery for NSCLC 1 cm or less in diameter: 75 patients underwent lobectomy (lobectomy in 71 and bilobectomy in 4), and 25 underwent limited resection (segmentectomy in 12 and wedge resection in 13). Most patients had a complete mediastinal lymphadenectomy. The lobectomy group had a 5-year overall survival of 71%, compared with 33% for the limited resection group ($P = 0.03$). Also, there was a nonsignificant trend ($P = 0.07$) in 5-year cancer-specific survival, favoring the lobar group at 92% versus 47%.

There were small but near-equal numbers of patients undergoing both segmentectomy and wedge resection in this study, which may have influenced the less favorable outcome of the sublobar group. Medical comorbidities may have also contributed to the reduced survival. Interestingly, on a subset analysis, the 5-year overall survival rate for segmentectomy was statistically superior to that for wedge resection ($57\%$ vs $27\%; P = 0.03$), as was the 5-year cancer-specific survival rate ($75\%$ vs $42\%; P = 0.04$). Moreover, a significant difference existed between the 5-year overall and cancer-specific survival rates for patients who underwent lobectomy and wedge resection, but not between those patients who underwent lobectomy and segmentectomy.

In 2005, Okada et al. reported a large retrospective study of 1272 patients undergoing surgery for NSCLC in order to determine outcomes based on the type of procedure and size of tumor. Table 2 summarizes the results of this study. For tumors less than 3 cm, there was no significant difference in 5-year cancer-specific survival among patients undergoing lobectomy and segmentectomy. However, for patients undergoing wedge resection, survival was significantly worse for tumors larger than 2 cm. The appropriateness of sublobar resection for small lung tumors was recently addressed in a report by Kates et al. This study evaluated 2090 stage I NSCLC tumors 1 cm or less from the Surveillance Epidemiology and End Results registry. Of these, 688 patients underwent sublobar resection. There was no difference in overall or lung cancer-specific survival between the sublobar resection and lobectomy groups. Also, when propensity score analysis was undertaken to account for baseline differences, there was no significant difference.

### Sublobar Resection With Brachytherapy

Whereas sublobar resection has the theoretical advantage of preserving pulmonary function in high-risk patients, the associated higher recurrence rates are of concern with this approach. In an effort to improve the surgical margin for local control, investigators have used adjuvant intraoperative brachytherapy using $^{125}$I seeds. Two techniques have been used. In the first technique, absorbable polyglactin (Vicryl) sutures containing brachytherapy seeds are placed parallel to the surgical staple line. With the second technique, these seed-containing sutures are incorporated into an absorbable polyglactin mesh, which is then placed over the staple line after resection.

Before this, adjuvant external beam radiotherapy had been used by some groups to improve local control after sublobar resection. However, physiologic lung movement and the 3-dimensional irregularity of the staple line after sublobar resection limit the ability to deliver radiation effectively to a small area around the resection margin. This, in turn, may lead to increased and unwanted radiation exposure of normal areas of the lung, especially in the compromised patients who are usually treated with sublobar resection. In a study coordinated by the Cancer and Leukemia Group of patients who underwent video-assisted wedge resection and “postage-stamp” radiotherapy, extended treatment fields were needed because of the extent of the postoperative staple line. Also, 11% of the patients treated with radiotherapy developed severe dyspnea, and 4% developed moderate pneumonitis. These findings illustrate the difficulties in delivering external beam radiation therapy to these compromised patients.

Mesh or suture brachytherapy offers several advantages over external beam radiotherapy. Direct placement of the radiation source at the time of resection minimizes the radiation exposure to other parts of the lung. Also, close apposition of the source to the area of resection reduces the total radiation dose required to achieve local control. Moreover, the 1-time placement of the brachytherapy prosthesis results in 100% patient compliance as it obviates the need for the patient to return to the hospital for subsequent treatments, as would be necessary with external beam radiotherapy. Currently, no incidents of significant radiation-induced toxicity have been reported in studies using this technique.

In 2003, Santos et al. reported a retrospective review of 102 patients treated with sublobar resection compared with 101 patients treated with sublobar resection and $^{125}$I mesh brachytherapy for stage I NSCLC. The local recurrence rate in the brachytherapy group was 2%, compared with 18.6% in the group treated with sublobar resection alone ($P = 0.0001$). Also, in that same year, Lee and colleagues reported their experience involving $^{125}$I suture brachytherapy after sublobar resection in 33 patients and demonstrated a 5-year overall and cancer-specific survival rates of 67% and 77%, respectively, for T1N0 tumors. The local recurrence rate in this series was 6.1%. Although it was less than traditionally reported with sublobar resection, this higher recurrence rate may have been due to a preference for wedge resections in this study, compared with a preference for segmentectomy in the study by Santos and colleagues.

In 2005, Fernando and colleagues reported a multicenter retrospective study of 291 patients with T1N0 NSCLC who underwent lobectomy (167 patients) or sublobar resection (124 patients). Of note, 60 patients in the sublobar resection group also underwent placement of $^{125}$I mesh brachytherapy. Among the patients in the sublobar group, the local recurrence rate was 3.3% for those who had adjunctive mesh brachytherapy compared with 17.2% for those who did not ($P = 0.012$). In the following year, Birdas and colleagues reported a retrospective study of 167 patients with stage IB NSCLC. One hundred twenty-six patients underwent lobectomy, and 41 were treated with sublobar resection (27 segmentectomies and 14 wedge resections) and $^{125}$I mesh brachytherapy. Local recurrence for the sublobar resection group was comparable to that of the lobectomy group (4.8% vs 3.2%; $P = 0.6$) and indicated that, even for larger stage I tumors, the addition of brachytherapy to sublobar resection can be beneficial.

The benefit from adjuvant brachytherapy is most likely its ability to improve the surgical margin. Therefore, the greatest

<table>
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<tr>
<th>TABLE 2. Five-Year Cancer-Specific Survival (From Okada et al)</th>
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<tr>
<td>After lobectomy</td>
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<td>After segmentectomy</td>
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<tr>
<td>After wedge resection</td>
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impact may be in those patients who are treated with close wedge resections rather than a wide wedge or segmental resection. The impact of margin on local recurrence rates has been previously demonstrated. El-Sherif et al. reported on 81 patients treated with sublobar resection. There were 41 tumors with a margin of less than 1 cm and 40 with a margin of 1 cm or greater. The margin significantly impacted local recurrence, with 14.6% of patients developing local recurrence when the margin was less than 1 cm compared with 7.5% of patients when the margin was 1 cm or more (P = 0.04). In another study, the impact of the ratio of margin to tumor diameter was evaluated. A margin-to-tumor ratio of less than 1 was associated with a significant increase in recurrence rates, compared with ratios of 1 or greater (25.0% vs 6.2%; P = 0.0014).

The American College of Surgeons Oncology Group has recently completed a study (Z4032) comparing sublobar resection with brachytherapy to sublobar resection alone. The primary endpoint of Z4032 is local recurrence and is expected to be reported in 2012. Tumor size and margin information has been collected, and the impact that this has on recurrence rates will be helpful in improving our understanding of how these factors interact.

Preserving Pulmonary Function With Sublobar Resection

Ultimately, the loss of pulmonary function is related to the amount of lung resected relative to the amount of healthy lung that remains. In addition, for high-risk patients with severe cardiopulmonary disease, mortality may eventually be a result of their comorbid medical conditions rather than the lung cancer. Therefore, sublobar resection as a “compromise” intervention for high-risk patients—to preserve pulmonary function—remains an important treatment option for local control. Even in the previously mentioned 1995 LCSG report, preservation of pulmonary function was demonstrated for patients who underwent sublobar resection, compared with lobectomy, at 6 months. At 12 to 18 months, there did not appear to be a benefit with sublobar resection. However, this may have been due to the loss of follow-up pulmonary function tests for many patients at this longer interval evaluation. Nevertheless, the increasing evidence of comparable outcomes between lobectomy and sublobar resection for small tumors has motivated surgeons to investigate the impact on postoperative function more thoroughly.

In a report by Keenan and colleagues in 2004, 201 patients were treated for stage I NSCLC with either segmentectomy or lobectomy. Notably, preoperative pulmonary function was reduced in the segmentectomy group (forced expiratory volume in 1 second [FEV₁] of 75.1% vs 55.3% for lobectomy group; P < 0.001). Statistically significant declines in pulmonary function were demonstrated at 1-year follow up in the lobectomy group (forced vital capacity [FVC] of 85.5% to 81.1%, FEV₁ of 75.1% to 66.7%, maximum voluntary ventilation 72.8% to 65.2%, and diffusion capacity of the lung for carbon monoxide (DLCO) of 79.3% to 69.6%). For the segmentectomy group, only the DLCO showed a statistically significant decline, suggesting better preservation of pulmonary function in the segmentectomy group, despite their more impaired baseline status.

Harada and colleagues reported a study in 2005 focused on determining the degree of postoperative loss in pulmonary function in patients undergoing surgery for early-stage NSCLC. Thirty-eight patients underwent segmentectomy, and 45 underwent lobectomy. There were no preoperative differences in pulmonary function tests between the 2 groups. Regression analysis enabled these investigators to demonstrate a positive correlation between the number of resected segments and loss of FVC and FEV₁ at both 2 and 6 months of follow up. In addition, postoperative reductions in FVC and FEV₁ were significantly less for the segmentectomy group.

Moreover, in the previously mentioned 2006 report by Okada and associates, preoperative and postoperative PFTs were available for 354 patients undergoing surgery for NSCLC 2 cm or less, including 168 patients who underwent segmentectomy, 168 patients who underwent lobectomy, and 18 patients who underwent wedge resection. Reductions in lung function correlated with extent of resection, noted by decreases in both FVC and FEV₁. Interestingly, statistically significant differences were demonstrated in the loss of pulmonary function between the lobectomy and sublobar resection groups, further suggesting the reduced loss of function for sublobar resection.

Finally, a preliminary report of the American College of Surgeons Oncology Group Z4032 randomized trial—which compared stage I NSCLC patients treated either with sublobar resection or sublobar resection and brachytherapy—analyzed the impact of brachytherapy on 3-month pulmonary function tests, dyspnea score, and perioperative (30-day) respiratory-specific complications in this high-risk patient population. Adjacent intraoperative brachytherapy did not significantly worsen pulmonary function or dyspnea at 3 months, nor was it associated with increased perioperative respiratory adverse events.

FUTURE DIRECTIONS

At present, lobectomy remains the treatment of choice for stage I NSCLC. Yet, as CT screening for lung cancer becomes more commonplace, the frequency of detecting smaller lung cancers will increase. For these tumors, sublobar resection seems to provide outcomes comparable to lobectomy, and early evidence demonstrates that brachytherapy may enhance local control. There is an ongoing national randomized multicenter trial comparing lobectomy to sublobar resection in patients with small peripheral stage IA NSCLC (cancer and leukemia group B 140503). This study will help validate the role of sublobar resection as a primary treatment option for patients who can tolerate a lobectomy. In addition, the ACOSOG Z4032 trial will help define the role of brachytherapy in sublobar resection for the local control of lung cancer.

Moreover, although it is the concern for increased local recurrence that influences the selection of lobectomy as the standard treatment for patients with T1N0 lung cancers who can tolerate the operation, sublobar resection as a “compromise” operation for high-risk patients is reasonable, safe, and associated with good survival particularly for small tumors. For the high-risk operable patient, sublobar resection should be considered the procedure of choice.

Alternative therapies such as stereotactic body radiation therapy and thermal ablation are available and gaining popularity for these patients, as described elsewhere in this text. However, varying definitions of local recurrence in the surgery and radiology literature, as well as differences in patient selection, preclude a fair comparison of these therapies. For instance, in the surgical literature, local recurrence usually includes recurrence within the same lobe, sometimes another lobe within the same ipsilateral lung, and also regional (hilar and sometimes ipsilateral mediastinal) nodes. This definition differs from reports of nonresectional modalities, where local recurrence is generally limited to recurrence within, or immediately adjacent to, the lung tumor that was treated.

In addition, when resection is performed, lymph node dissection or sampling can also be undertaken, which can enhance local control, impact survival, and identify patients with occult metastic disease that could benefit from other therapies. On the other
hand, particularly for smaller tumors, there may be a benefit with a nonresectional approach in terms of lower morbidity that may result in “as-good” outcomes when considering therapy for a high-risk patient. This important issue will be investigated in an upcoming randomized study (ACOSOG Z4090/RTG1 102.1) that will compare sublobar resection to SBRT for high-risk operable patients with early-stage lung cancer. This study will be useful as similar risk patients will be compared, using the same end-point definitions, and will significantly increase our ability to make treatment recommendations for high-risk patients with lung cancer.

REFERENCES