Pattern of Metastasis Outside Tumor-Bearing Segments in Primary Lung Cancer: Rationale for Segmentectomy

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**Background.** Patterns of intrapulmonary metastasis, particularly metastasis outside tumor-bearing segments, were investigated in lung cancer patients to address the rationale for segmentectomy.

**Methods.** In a consecutive series of patients who underwent resection of two or more pulmonary segments for primary lung cancer, intrapulmonary spread patterns, such as segmental/intersegmental node metastasis and pulmonary parenchymal metastasis, were pathologically examined.

**Results.** Eligible 244 lesions included 167 adenocarcinomas, 66 squamous cell carcinomas, and 11 large cell carcinomas. Pathologic stages included 0 to IA (n = 111), IB (n = 56), IIA (n = 31), IIB (n = 20), IIIA (n = 23), and IIIB to IV (n = 20); and N1 (n = 23) and N2 (n = 22). Intrapulmonary spread was observed in 24 cases (9.8%). Of these, metastasis outside tumor-bearing segments was only observed in 4 cases (1.6%), and such cancer spread was more frequently seen in cases with extrapulmonary (hilar to mediastinal) nodal metastasis (7.9%) than in cases without extrapulmonary metastasis (0.5%; p = 0.01). Metastasis outside tumor-bearing segments was not observed in 64 tumors with pure or mixed ground glass opacity features on computed tomography. Although tumor location (peripheral or central/intermediate) was not related to the incidence of metastasis outside tumor-bearing segments, intrapulmonary spread was observed in only 1 of 52 peripheral small (<20 mm) tumors.

**Conclusions.** Metastasis outside tumor-bearing segments is rarely observed in cases with tumors (1) without extrapulmonary nodal metastasis and (2) with ground glass opacity or peripheral small (<20 mm) features.

(Lobectomy with systematic nodal dissection has been a standard surgery for non-small cell lung cancer (NSCLC) for more than 50 years [1], and sublobar resection such as wedge resection or segmentectomy [2, 3] is an alternative for compromised patients as it was proved that sublobar resection is inferior to lobectomy in terms of local control as well as prognosis by the historical randomized controlled study conducted by the Lung Cancer Study Group in 1980s [4]. However, a great interest in limited resections has kept growing since small-sized and peripheral lung cancer has increased over time. A number of studies performed in the 1990s and 2000s demonstrated that segmentectomy is more radical than wedge resection [5–8], and segmentectomy would be as curative as lobectomy if peripheral and small-sized tumors were selected [9]. Now limited resections for such a type of NSCLC is one of the most important concerns of thoracic surgeons.

In 1889, William Ewart first described the units of bronchopulmonary segments, and Churchill and colleagues [10] stated that “the bronchopulmonary segment may replace the lobe as the surgical unit of the lung,” based on their experience of lingular segment resection in 1939. Foster-Caster and Hoyle [11] reevaluated this theory based on radiologic findings, and defined the bronchopulmonary segment as that area of the lung supplied by a principal branch of a lobar bronchus. Nevertheless, the lymphatic spread hypothesis remains based on the traditional nodal cascade spread theory [12, 13]. For instance, lymphatic spread patterns should be primarily prograde; this theory provides the rationale for segmentectomy as a treatment for primary lung cancer. However, recently it has also become accepted that no definitive
intrathoracic lymphatic spread pattern exists [14]; thus, whether segmentectomy is a feasible treatment for lung cancer considering intrapulmonary lymphatic spread patterns remains to be clarified. Furthermore, parenchymal metastasis must also be considered in addition to lymph node metastasis as a cause of lymphatic spread [15].

The aim of this study was to better understand the biology of intrapulmonary and regional lymph node metastasis of NSCLC by examination of intrapulmonary spread patterns, including nodal and parenchymal metastasis, in resected specimens.

Material and Methods

Patients

The Ethics Committee of Chiba University Graduate School of Medicine approved this research (no. 1589). From September 2009 to August 2012, a consecutive series of 346 patients with 406 lesions undergoing pulmonary resection for treatment of lung cancer was evaluated, and clinical and pathologic data were collected in a prospective setting. The TNM staging and lymph node station numbers were determined according to the seventh edition of the TNM classification for lung cancer (Union for International Cancer Control-7) [16]. The exclusion criteria of this study were resection of single segment or less, no systematic sampling or dissection during the surgery, ipsilateral multiple lesions, small cell lung cancer and rare histologic type of NSCLC, and preoperative cancer treatment including induction chemotherapy or chemoradiotherapy.

In all patients, radiologic findings and locations of tumors were defined by thin-section computed tomography (CT), which involved multidimensional slicing and reconstruction into axial, coronal, and sagittal views. Tumor location was also classified into three loci based on three-dimensional imaging: peripheral type was defined as the center of tumor being located in the outer third layer of the whole lung; central type was defined as the center of tumor being located in the inner third layer; and intermediate type was defined as the center of tumor being located between peripheral type and central type. Tumor CT findings were read by two or more radiologists and assigned to one of the following three groups based on axial CT imaging in a preoperative conference that all general thoracic surgeons and radiologists attend: pure ground grass opacity (GGO) type as 100% GGO appearance; solid type as 100% solid appearance without any GGO components; and mixed GGO type as any other patterns (any combination of solid and GGO components). Clinical information was collected from medical charts.

Pathologic Examination of Lymph Nodes

After identification of each bronchus and intersegmental veins that are segmental borders in the resected specimens, intrapulmonary nodes, including intersegmental nodes (station 13) and segmental nodes (station 14), were dissected by a well-trained thoracic surgeon immediately after surgery. Station 13 and station 14 nodes were identified and separately recorded as being inside or outside the tumor-bearing segment, and were subjected to pathologic examination (Fig 1). We also separately recorded extrapulmonary nodes, including hilar nodes (hilar, station 10; interlobar, station 11; and lobar, station 12) and mediastinal nodes (stations 1–9). We defined “skip N2 metastasis” as a mediastinal nodal metastasis without any hilar, lobar, or intrapulmonary node involvement. Intersegmental borders were determined by detection of intersegmental veins. The lung parenchyma was inspected after formalin fixation by pathologists, the resected lung was cut into 1-cm slices in the axial plane, and the pathologic parenchymal metastasis (pm) status was also diagnosed and recorded.

These prospectively collected clinical and pathological data were retrospectively analyzed with respect to the relationships between clinicopathologic features including tumor location, cancer spread pattern in the intrapulmonary area, and cancer spread pattern outside the tumor-bearing segment.

Statistical Analysis

Frequency analysis was performed using the $\chi^2$ test. The Wilcoxon rank sum test was applied to continuous data. Data were analyzed using JMP 10 software (SAS Institute, Cary, NC). All $p$ values were based on a two-tailed hypothesis test; a $p$ value of less than 0.05 was considered to have statistical significance.
Results

Patient Characteristics

In a total of 406 lesions treated during the study period, 27 double cancers and 3 triple cancers were included. Based on the exclusion criteria, 162 lesions were omitted from the analysis for the following reasons: resection of single segment or less (n = 58), no systematic sampling or dissection (n = 9), ipsilateral multiple lesions (n = 49), small cell lung cancer and rare histological type of NSCLC (n = 12), and preoperative anticancer treatments (n = 34). Consequently, 244 lesions were subjected to the analysis described below.

The characteristics of eligible lesions are summarized in Table 1. The 244 eligible lesions were present in 170 male patients and 74 female patients, and the average patient age was 68.4 ± 8.3 years. Primary tumor locations included peripheral type (n = 167), intermediate type (n = 49), and central type (n = 28). The CT findings were pure GGO tumors (n = 20), mixed GGO tumors (n = 44), and solid-type tumors (n = 180). Tumors were located in the right lung in 138 cases and in the left lung in 106 cases. Tumor location details are shown in Figure 2. The cohort included 167 adenocarcinomas, 66 squamous cell carcinomas, and 11 large cell carcinomas. Pathologic stages included stage 0 to IA (n = 111), stage IB (n = 56), stage IIA (n = 31), stage IIB (n = 20), stage IIIA (n = 23), and IIIB to IV (n = 3). Pathologic nodal metastasis was observed in 48 lesions (20%), including 26 pN1 and 22 pN2 cases.

Extrapulmonary and Intrapulmonary Metastasis

Among 48 cases with nodal metastasis, extrapulmonary nodal metastases were identified in 38 lesions, and occurred more frequently in lesions in intermediate/central locations (Table 2). Among the 38 lesions with extrapulmonary node metastasis, intermediate/central type and solid type lesions comprised a larger proportion than they did among the 206 lesions without extrapulmonary node metastasis. Pathologically, lymphatic permeation and vessel invasion were more frequently detected in lesions with extrapulmonary node metastasis than in lesions without such metastasis, whereas no difference in pleural invasion was observed between the two groups (Table 2).

Metastatic intrapulmonary nodes were observed in 20 lesions, representing 42% of lesions with nodal metastasis (Table 2). Intrapulmonary parenchymal metastasis (pm1) occurred in five lesions (2.0%), one of which was simultaneously accompanied by extrapulmonary nodal metastasis. All pm1 lesions occurred in tumor-bearing
These five lesions were poorly to moderately differentiated adenocarcinomas. Altogether, intrapulmonary spread was observed in 24 lesions (9.8%), of which 19 were segmental/intersegmental nodal metastases, 4 were parenchymal metastases, and 1 was both. Of the 24 lesions, 12 (50%) were associated with extrapulmonary node metastasis (Table 2); the other one was not associated with any nodal metastasis or parenchymal metastasis, and represented only 0.5% of the total lesions (1 of 206) without extrapulmonary metastasis. Among all lesions, primary tumors were most commonly solid type, whereas primary tumor locations were not significantly associated with the incidence of the type of metastasis (Table 3).

Metastasis outside the tumor-bearing segment was observed in only 4 cases (17%), representing only 1.6% all lesions (Table 2). Of the 4 cases, intermediate/central type tumors, and in solid type lesions compared with their respective counterparts (Tables 2 and 3).

Metastasis outside the tumor-bearing segment was observed in only 4 cases (17%), representing only 1.6% all lesions (Table 2). Of the 4 cases, one was associated with extrapulmonary node metastasis (Table 2); the other one was not associated with any nodal metastasis or parenchymal metastasis, and represented only 0.5% of the total lesions (1 of 206) without extrapulmonary metastasis. Among all lesions, primary tumors were most commonly solid type, whereas primary tumor locations were not significantly associated with the incidence of the type of metastasis (Table 3). In the 4 cases with metastasis outside the tumor-bearing segment, interestingly, all primary tumors were located in the left lung, three being in the left upper lobe.

### Peripheral Small Tumors

Of the 167 peripheral type lesions, 52 (31%) were 20 mm or less in diameter. Among these, nodal metastasis was observed in 9.6% of lesions (5 of 52), all of which were solid type and were associated with multiple nodal

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#### Table 2. Clinical and Pathologic Factors of Cases With and Without Extrapulmonary Node Metastasis

<table>
<thead>
<tr>
<th>Clinical and Pathologic Factors</th>
<th>All</th>
<th>(+)</th>
<th>(−)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>244</td>
<td>38</td>
<td>206</td>
<td>0.04</td>
</tr>
<tr>
<td>Intermediate/central</td>
<td>77</td>
<td>18</td>
<td>59</td>
<td>0.4</td>
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<tr>
<td>Solid appearance</td>
<td>180</td>
<td>37</td>
<td>143</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average tumor size, mm</td>
<td>30.7 ± 15.1</td>
<td>33.4 ± 14.8</td>
<td>30.2 ± 16.1</td>
<td>0.11</td>
</tr>
<tr>
<td>COPD lung</td>
<td>47</td>
<td>7</td>
<td>40</td>
<td>1.00</td>
</tr>
<tr>
<td>Interstitial pneumonia lung</td>
<td>26</td>
<td>3</td>
<td>23</td>
<td>0.15</td>
</tr>
<tr>
<td>Intrapulmonary nodes (stations 13, 14)</td>
<td>20</td>
<td>11</td>
<td>9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Parenchymal metastasis (pm1)</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>0.57</td>
</tr>
<tr>
<td>Intrapulmonary spread (stations 13, 14, or pm1)</td>
<td>24</td>
<td>12</td>
<td>12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metastasis inside tumor-bearing segment (stations 13, 14, pm1)</td>
<td>20</td>
<td>9</td>
<td>11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metastasis outside tumor-bearing segment (stations 13, 14, pm1)</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Lymphatic permeation (+)</td>
<td>39</td>
<td>18</td>
<td>21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vessel invasion (+)</td>
<td>88</td>
<td>25</td>
<td>63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any pathologic pleural invasion (+)</td>
<td>66</td>
<td>14</td>
<td>52</td>
<td>0.17</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease.

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#### Table 3. Tumor Localization, Computed Tomography Findings, and Intrapulmonary Spread

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All</th>
<th>Peripheral</th>
<th>Intermediate/ Central</th>
<th>p Value</th>
<th>Pure/Mixed GGO</th>
<th>Solid</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>244</td>
<td>167</td>
<td>77</td>
<td></td>
<td>64</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary nodes (stations 1–12)</td>
<td>38</td>
<td>20</td>
<td>18</td>
<td>0.04</td>
<td>1</td>
<td>37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hilar and lobar nodes (stations 10–12)</td>
<td>30</td>
<td>15</td>
<td>15</td>
<td>0.03</td>
<td>1</td>
<td>29</td>
<td>0.0014</td>
</tr>
<tr>
<td>Skip N2</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>0.71</td>
<td>0</td>
<td>8</td>
<td>0.12</td>
</tr>
<tr>
<td>Intrapulmonary nodes (stations 13, 14)</td>
<td>20</td>
<td>9</td>
<td>11</td>
<td>0.02</td>
<td>1</td>
<td>19</td>
<td>0.03</td>
</tr>
<tr>
<td>Parenchymal metastasis (pm1)</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>0.04</td>
<td>0</td>
<td>5</td>
<td>0.33</td>
</tr>
<tr>
<td>Intrapulmonary spread (stations 13, 14, or pm1)</td>
<td>24</td>
<td>10</td>
<td>14</td>
<td>0.005</td>
<td>1</td>
<td>23</td>
<td>0.007</td>
</tr>
<tr>
<td>Metastasis inside tumor-bearing segment (stations 13, 14, pm1)</td>
<td>20</td>
<td>8</td>
<td>12</td>
<td>0.01</td>
<td>1</td>
<td>19</td>
<td>0.03</td>
</tr>
<tr>
<td>Metastasis outside tumor-bearing segment (stations 13, 14, pm1)</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0.59</td>
<td>0</td>
<td>4</td>
<td>0.57</td>
</tr>
</tbody>
</table>

GGO = ground glass opacity.
metastasis in extrapulmonary nodes. Spread outside tumor-bearing segments was not observed, whereas spread inside tumor-bearing segments was observed in 1 case (1.4%). In lesions without extrapulmonary node metastasis, no intrapulmonary spread was observed in association with peripheral small (≤20 mm) tumors. Among the 167 peripheral type lesions, 103 (62%) had a diameter of 30 mm or less. Nodal metastasis was observed in 10 of these 103 lesions (9.7%), all of which were solid type primary tumors.

**Tumor Spread Pattern**

A flowchart based on tumor-spread pattern is illustrated in Figure 3. Cancer spread outside tumor-bearing segments in patients with hilar or mediastinal nodal metastasis occurred in 7.9% cases (3 of 38), whereas the frequency was 0.5% (1 of 206) among patients without hilar or mediastinal nodal metastasis; this result is consistent with the concept of the bronchopulmonary segment. As such, the 205 lesions might be completely resected by segmentectomy following the right path in Figure 3. The extrapulmonary node metastasis is searchable at the time of surgery; therefore, this would be a crucial condition for selection of candidates for segmentectomy. Among these 205 lesions, 194 lesions without intrapulmonary spread might be radically removed by wedge resection; however, such metastasis can only be demonstrated through detailed pathologic examination. There would be no doubt that lobectomy or more substantial surgery should be used in the 38 cases with extrapulmonary nodal metastases (left half of the path of Fig 3). However, 35 of the 38 cases (92%) were not accompanied by spread outside the tumor-bearing segment.

**Comment**

It is very important to better understand intrapulmonary spread pattern of NSCLC because spread to outside of tumor-bearing segment leads to locoregional recurrence in case of segmentectomy; that is now paid great attention as a novel surgical modality for peripheral small NSCLC. In case no lymph node metastases are found in resected specimens, patients would not undergo any treatments until local recurrence appears even if they have metastasis outside of tumor-bearing segments. The historical randomized trial conducted by the Lung Cancer Study Group [4] clearly indicated that local recurrence after sublobar resection is associated with unfavorable survival. In this study, the intrapulmonary spread pattern of NSCLC was fully examined using resected specimens.

Nodal metastasis to the intrapulmonary region is a common pattern of spread, and nodal metastasis to stations 12 and 13 has been reported to occur in 38.5% of pN1 patients [17]. Furthermore, the prognosis of pN1 patients with only intrapulmonary nodal metastasis (ie, stations 13 and 14) has been reported to be as poor as that for pN1 patients without intrapulmonary nodal metastasis [18]. Thus, the indication for limited resection should be carefully defined to avoid failure in removal of intrapulmonary metastatic lesions. In particular, metastasis outside tumor-bearing segments is an issue to be resolved. In this study, we analyzed the intrapulmonary spread pattern by nodal and parenchymal inspection of resected lungs; metastasis outside tumor-bearing segments was observed in only four lesions (1.6% of total lesions), and the clinicopathologic features of these lesions included primary tumor in the left upper lobe (75%), solid tumor (100%), and multiple nodal metastases in extrapulmonary nodes (75%).

We observed one lesion located in the superior lingular segment (S4) with intrapulmonary metastasis outside the tumor-bearing segment that was not associated with any other metastasis. Topol and associates [19] demonstrated the existence of a nodal metastatic tract across the intersegmental plane between the superior and inferior lingular segments in 2 of 135 examinations of cadaveric lungs. The tract may function as another lymphatic metastatic route. Even though this tract is very rare, it should be kept in mind when considering sublobar resection. Another explanation for this lesion not being associated with any other metastasis is remodeling of lymphatics due to chronic lung disease [20], as the patient had chronic obstructive pulmonary disease and interstitial pneumonia.

Solid type tumors comprise 96% of lesions (23 of 24) with intrapulmonary metastasis, 100% (5 of 5) with parenchymal spread, and 100% (4 of 4) with metastasis

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**Fig 3. Tumor spread pattern.** The algorithm shows a cascade based on three tumor-spread processes: (1) extrapulmonary nodal metastasis, (2) intrapulmonary spread, and (3) metastasis outside tumor-bearing segments. The number of lesions that fulfill each condition are shown, from the top: total lesions (black numbers), peripheral lesions (green numbers), and 20 mm or less peripheral lesions (red numbers). The single patient with metastasis on the outside of the tumor-bearing segment without any hilar or mediastinal nodal metastasis is noted by an asterisk (*).
outside tumor-bearing segments. In the literature, 16% of solid type tumors of 20 mm or less are associated with nodal metastasis [21]. Consequently, solid tumors should be carefully considered for limited surgery.

Small tumor size should be a required condition for limited surgery in consideration of surgical margins. Okada and associates [22] suggested segmentectomy limited surgery in consideration of surgical margins. Okada and associates [22] suggested segmentectomy with lymph node assessment as an alternative to lobectomy in patients with 20 mm or less NSCLC, and the present results support this theory. Several studies have advocated that candidates include a tumor size of 30 mm or less [7, 9, 22]. In the present study, of 103 lesions with a diameter of 30 mm or less, 3 intrapulmonary spread lesions (2.9%) without any extrapulmonary nodal metastasis were observed. In contrast, no such lesions were observed among 52 lesions with a diameter of 20 mm or less. Thus, nonanatomic sublobar resection for peripheral tumors 30 mm or less could allow the tumor to remain. In our series, 5 patients of 27 with mixed GGO tumors more than 20 mm underwent segmentectomy owing to inadequate pulmonary reserve. Recently, Asamura and colleagues [23] reported that 2 cm to 3 cm (T1b) adenocarcinoma with 0.5 or less consolidation/tumor diameter ratio showed a significantly favorable prognosis, with 96.4% survival at 5 years after lobectomy in a prospective observational study (JCOG2001). Such tumors may be well indicated for sublobar resection. Now the Japanese Clinical Oncology Group plans to start a new prospective study for sublobar resection. Now the Japanese Clinical Oncology Group plans to start a new prospective study for sublobar resection. Finally, the optimal candidacy for limited resection, particularly segmentectomy, must be addressed. Development of strategies for judging the presence of such metastasis might increase the number of candidates for segmentectomy. Computed tomography is one of the tools used to select candidates for segmentectomy, as reported previously [26]. In 64 pure/mixed GGO type lesions in this study, no spread outside the tumor-bearing segment was observed, whereas cancer spread inside the tumor-bearing segment was seen in one lesion. In 52 peripheral small size (≤20 mm) tumors without extrapulmonary nodal metastasis, no intrapulmonary metastasis was found; therefore, such lesions also appear to be good candidates for segmentectomy from the viewpoint of intrapulmonary spread pattern.

In conclusion, cancer spread to the outside of the tumor-bearing segment is infrequently observed in lung cancers when the tumor is not associated with extrapulmonary nodal metastasis, in pure-mixed GGO lesions or in peripheral small (≤20 mm) lesions.

The authors sincerely thank all of the thoracic surgeons in the Department of General Thoracic Surgery, Chiba University Hospital, for their cooperation in data collection.

References

INVITED COMMENTARY

The work of Sakairi and associates [1] provokes thoughts on our basic concepts of “adequacy of surgery” fostered from the Halstedian “centrifugal pattern” of cancer spread [2]. Although Halsted’s “complete surgical management” concept was challenged even after its inception [3], this deeply rooted dogma of our surgical heritage is a hard principle from which to depart.

The authors provide rather convincing data carefully assimilated from a large clinicopathologic evaluation of anatomic resections of 2 or more pulmonary segments for what I perceive was believed to be clinical stage I primary lung cancer amenable to sublobar resection. They conclude that the likelihood of tumor spread beyond the confines of the parenchyma of the “extended segmentectomies” of this series was very unlikely.

Among patients with small peripheral lesions (<2.0 cm in diameter) or with predominant ground-glass lesions by computed tomographic imaging, the occurrence was negligible. However, the occurrence was greatest among those patients found on pathologic review to have had extrapulmonary nodal metastases (15.5% of the entire group).

I come away with a few thoughts and further questions regarding this analysis. It appears that the primary determining factors related to reliance on segmentectomy as definitive local therapy for clinical stage I lung cancer are tumor size and morphologic characteristics of the lesion seen on computed tomography. The primary negative determinant is the identification of intraoperative determination of extraparenchymal nodal metastases.

The similarity of these findings to those of sentinel node evaluation for stage I and stage II breast cancer in determining the use of axillary lymph node dissection is striking. Because no clinical outcomes related to these anatomic/pathologic findings are provided in this work, we conjecture that the use of more radical surgical procedures for a positive “sentinel node” finding may have the equivocal long-term outcome as noted with lesser surgical procedures for breast cancer [4].

Although local failure can be an important consideration for the minority of patients undergoing anatomic segmentectomy for presumed favorable peripheral stage I lung cancers, these recurrences and the presence of nodal metastases are largely harbingers of an aggressive phenotype of disease beyond the boundaries of the surgeon’s knife.

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References