Small Cell Lung Cancer Presenting as a Solitary Pulmonary Nodule*

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Small cell lung cancer (SCLC) is a highly malignant tumor that is almost always metastatic at the time that it is diagnosed. Typically, its radiographic appearance is that of a lung mass with associated bulky hilar and/or mediastinal adenopathy. Infrequently, SCLC presents as a solitary pulmonary nodule (SPN).

Although SCLC presenting as an SPN is uncommon,1,2 it nevertheless is an important entity because it represents a potentially curable neoplasm. This review summarizes the literature on SCLC presenting as an SPN (SCLC-SPN) and evaluates the various treatment modalities and the prognosis of patients with this entity.

DEFINITION

An SPN is a single spherical or oval intrapulmonary density not exceeding 6 cm in its largest diameter.3,4 Many authors insist that only lesions surrounded by normal lung parenchyma be included in this definition.3,4 Such lesions are usually fairly discrete but may have smooth or lobulated contours and may be calcified or cavitated.5 The differential diagnosis of an SPN encompasses a wide variety of benign and malignant conditions.6 Included among these is lung cancer, including the small cell variant. By definition, patients with radiographic or pathologic evidence of hilar or mediastinal adenopathy are excluded.

INCIDENCE

The overall incidence of malignancy in SPNs has been estimated to be approximately 20 percent.6,7 In surgical series, in which many benign lesions have been excluded clinically, 30 to 50 percent are reported to be malignant.8 Most such cases are adenocarcinoma or squamous cell carcinoma, with approximately equal frequency.1,9 Less commonly, large cell carcinoma or SCLC is found.1 In the Veterans Administration-Armed Forces Cooperative Study,1 each of lung cancers presenting as an SPN were SCLC. More recently, six cases of SCLC were identified among 50 (12 percent) cases with SPNs detected on screening radiographs by the Mayo Lung Project.9

Conversely, Quoix et al2 found that approximately 4 percent of all SCLCs presented as an SPN. In the New York Lung Cancer Detection Program, two of 27 (7 percent) SCLCs found by screening were pathologic T1N0 tumors.10

CLINICAL FEATURES

The clinical features of patients with SCLC-SPN are indistinguishable from those with non-small cell carcinoma (NSCLC).2,11 Most patients are men in their sixth or seventh decade with a history of heavy cigarette consumption. Unlike the majority of patients with SCLC, these individuals are usually asymptomatic, the diagnosis being made when a peripheral mass without hilar or mediastinal adenopathy is detected on a routine chest radiograph (Table 1). Although SCLC is considered a rapidly proliferating neoplasm, cases have been recognized in which, in retrospect, an SPN of this type had been present without clinical suspicion seven to 22 months earlier.2 Most often the diagnosis is made only when an asymptomatic pulmonary nodule is resected surgically.

STAGING AND CLINICAL EVALUATION

Accurate clinical and pathologic staging is important in SCLC-SPN because it may influence therapy as well as the physician's ability to estimate a patient's prognosis. Although most patients are asymptomatic, careful evaluation may identify, and thus "up-stage" individuals with occult metastatic disease.12-14 This

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process, known as stage migration or the Will Rogers phenomenon, serves to improve the apparent outcome of remaining patients with true SPNs, since a number of individuals with detectable metastases and a poorer prognosis are excluded.

The utility and histologic specificity of transthoracic needle biopsy for diagnosis in patients with SPNs has been addressed elsewhere.\textsuperscript{15} Although histologic differentiation between SCLC and NSCLC is considered to be relatively straightforward, this may not be the case if a scant cytologic specimen is obtained.\textsuperscript{16} Since, in most instances, surgical resection would likely be attempted whether the biopsy showed SCLC or NSCLC or was nondiagnostic, we suggest that transthoracic needle aspiration not be performed in these patients. In certain patients (eg, one with a pulmonary nodule suspected of being a lung metastasis or those with significant comorbidity\textsuperscript{16,19}, a transthoracic needle aspiration may be performed, and an unsuspected diagnosis of SCLC might be obtained. Such a patient or one with SCLC on transbronchial biopsy of an SPN should undergo a metastatic workup before surgical resection is considered.

Computed tomography (CT) of the thorax may reveal large lymph nodes, particularly in the paratracheal and subcarinal areas, that were not suspected on chest radiograph.\textsuperscript{12} Liver metastases or unsuspected adrenal masses may be visualized with CT or ultrasonography.\textsuperscript{12}

In patients with suspected SCLC-SPN, bronchoscopy may reveal extrinsic compression due to unsuspected hilar or mediastinal adenopathy, but any specimen obtained will likely yield negative cytologic findings. When CT has suggested adenopathy, bronchoscopy may allow transbronchial (trastachaeal) needle aspiration to confirm the presence of tumor at an N1 or N2 level, thus obviating surgery.\textsuperscript{17}

Although CT of the brain and radionuclide bone scanning infrequently detect unsuspected metastases in patients with SCLC-SPN, these studies should be done to eliminate a potentially unnecessary thoracotomy.\textsuperscript{18} This is in contrast to what is usually recommended in cases in which an SPN has not been pathologically diagnosed or NSCLC has been established. Abnormal routine hematologic screening may prompt the physician to perform bilateral bone marrow aspiration and biopsy.

When the above-mentioned studies suggest localized disease, surgery should be considered. However, the final decision to proceed with surgery should be made only after careful consideration of the patient's age, associated medical conditions, pulmonary function, and personal preference.\textsuperscript{15}

Although not routinely recommended in NSCLC, mediastinoscopy should be performed prior to resection in patients with an SPN who have a preoperative diagnosis of SCLC. Even mediastinoscopy is not useful in diagnosis of N2 disease in about 25 percent of cases with SCLC and mediastinal metastases found at thoracotomy.\textsuperscript{14,19} Thus, careful mediastinal node dissection and labeling should be done at thoracotomy because of the therapeutic and prognostic implications of the information so obtained. In one study there was no difference in survival between clinical stages I, II and III, whereas pathologic evaluation and staging did show a prognostic difference between groups.\textsuperscript{20}

Frequently, SPNs are resected without a preoperative diagnosis or staging mediastinoscopy. If the diagnosis of SCLC is subsequently established, staging should then be completed by using CT of the thorax and brain, as well as radionuclide bone scanning and either CT or ultrasonography of the upper abdomen to the level of the adrenal glands. An attempt should be made to confirm histologically the presence of metastatic disease if the findings from these studies are abnormal and suggestive of metastases.

Pathologic Findings

Pathologically, only cases without histologic evidence of hilar or mediastinal adenopathy are "true" SPNs. This includes two TNM categories: T1N0M0 for tumors 3 cm or less in size and T2N0M0 for those greater than 3 cm.\textsuperscript{21}

Histopathologic subtyping of SCLC is a controversial issue. Interobserver agreement is poor in determining different subtypes\textsuperscript{22,23}, however, it is not certain

<table>
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<tr>
<th>Table 1—Comparison of &quot;Usual&quot; SCLC and SCLC-SPN</th>
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<td><strong>SCLC</strong></td>
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<tr>
<td>Incidence</td>
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<tr>
<td>Clinical features</td>
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<td>Radiologic findings</td>
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<td>Diagnosis</td>
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<td>Pathologic findings</td>
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<td>Treatment</td>
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*TTNA = transthoracic needle aspiration.
Table 2—Small Cell Subtypes in Surgical and Nonsurgical Series

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<tr>
<th>Subtype</th>
<th>Oat Cell (%)</th>
<th>Cell (%)</th>
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<td>Surgical series</td>
<td>145 (32)</td>
<td>296 (66)</td>
</tr>
<tr>
<td>Nonsurgical series</td>
<td>679 (66)</td>
<td>291 (25)</td>
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Values are numbers of cases (%) in the cited studies. Eight cases in the surgical series and 56 cases in the nonsurgical series were neither pure oat cell nor pure intermediate cell type.

how much of this is due to crush artifact and the availability of only small biopsy specimens for review. In fact, the consensus report of the International Association for the Study of Lung Cancer suggests discarding oat and intermediate subtypes. Nevertheless, it is our opinion that determination of subtype may still be useful in SCLC-SPN and in surgically resected SCLC.

In surgically resected SCLC (including those that are classified as SPNs), the intermediate (polyoidal) cell type predominates, whereas in nonsurgical series of SCLC two thirds are classified as the oat cell subtype of SCLC (Table 2). Although cell type does not appear to affect prognosis in most nonsurgical patients with SCLC, the intermediate subtype is associated with a superior prognosis in most surgical series. Peripheral lesions (including SPN) and stage N0 tumors were more often associated with the intermediate cell type. Six of seven long-term survivors with intermediate cell tumors in one series had peripheral SPNs. In another report, 28 of 87 tumors of the intermediate cell type were surgical stage I tumors, compared with only one of 19 oat cell tumors.

Electron microscopy and the use of biochemical markers may provide valuable information and assist in diagnosis and prognosis. Seven SCLC-SPN cases studied by Gephardt et al showed significant neuron-specific enolase activity but less prominent and more variable staining for carcinoembryonic antigen and cytokeratins.

Patients with SCLC who have ultrastructural features usually associated with NSCLC may have a superior prognosis. These features are more often seen with the intermediate cell subtype than with the oat cell subtype. Thus, the absence of neurosecretory granules, keratin positivity, and the presence of epithelial membrane antigen have each been associated with improved survival in SCLC. It remains to be determined whether these markers will be equally valuable in SCLC-SPN.

Histologic evaluation of resected nodules may occasionally reveal mixed tumors, with variable amounts of SCLC and NSCLC in the same specimen. A controversy about resectable cases is whether such mixed histologic features influence prognosis compared with cases with pure SCLC features.

Well-differentiated neuroendocrine carcinoma, atypical carcinoids, and carcinoids can present as an SPN and may initially be misdiagnosed as SCLC. These tumors are usually curable by resection; therefore, erroneously including them will falsely improve the outcome in any series of SCLC-SPN patients.

**TREATMENT**

**Surgery**

Although surgery is not recommended for most patients with SCLC, it is potentially curative for those presenting with an SPN. The biology of SCLC-SPN may not be the same as that of other forms of SCLC, and therefore resection may yield survival benefits similar to those for NSCLC. Moreover, even when chemotherapy and/or radiotherapy is also employed, surgery may serve to eliminate resistant or NSCLC clones, as well as to remove the area of greatest tumor bulk prior to commencing use of these modalities. All areas of macroscopic disease may have been eliminated without any effect on bone marrow reserves, and intensive adjuvant therapy can then deal with the microscopic residual tumor.

Despite these theoretical advantages, the role of surgery for patients with limited SCLC, including those with an SPN, has not been firmly established. Although some authors state that the benefit of surgery is evident, others are more cautious in their conclusions. Studies comparing the effect of initial surgery in patients with limited SCLC suffering from being retrospective, having inadequate staging of lymph nodes, and having a possible selection bias that does not allow for valid comparisons between groups. For instance, Shepherd et al showed a superior survival in surgical patients with limited SCLC compared with those who did not undergo surgery, yet almost half (9/19) in the nonsurgical group were surgery “refusals.” Fifteen other patients in their series of 72 SCLC surgical candidates ultimately became ineligible for resection because of poor response to chemotherapy, poor medical condition, or treatment-related death.

There are three reports in which patients with SCLC-SPN were specifically identified as the group under study. Unfortunately, these reports are limited by incomplete surgical pathologic staging. Moreover, insufficient data are available for us to accurately predict survival in patients treated solely with surgery and patients in whom surgery was not employed. More information is available, however, for the broader category of patients with stage I SCLC.

In Table 3 we have compiled life-table survival estimates for patients with stage I SCLC treated with...
surgery (with or without adjuvant therapy), using pooled data from several studies. These data are shown graphically in Figure 1. The results suggest that good survival rates can be expected in the short term. However, the 40 to 53 percent survival at 60 months, although superior to that for the general category of limited SCLC, is not as good as that for stage I NSCLC. Thus, while surgery may be efficacious, additional therapy must be considered if long-term survival is to be improved.

Chemotherapy

In the previously cited articles on SCLC-SPN, chemotherapy was not administered to 30 of the 47 (64 percent) patients, yet many of these individuals had long-term survival. Nevertheless, the lack of a universally good prognosis following resection alone and the findings of Matthews et al. suggest that adjuvant therapy is indicated in order to eliminate micrometastatic foci of disease. In the past decade, effective chemotherapy has been widely used in SCLC. The timing of such therapy in relationship to resection is unclear in those rare patients suitable for surgery who have a preoperative diagnosis of SCLC. Preoperative chemotherapy has the appealing advantage of allowing one to judge response with CT and thus to discontinue or limit potentially toxic therapy in patients without observable benefit. Generally, however, surgery is the preferred initial treatment, and frequently the diagnosis of SCLC is made only at the time of resection of an SPN. We therefore recommend postoperative chemotherapy with the use of combinations known to be effective in the limited-disease stage of SCLC. These include cisplatin and etoposide; doxorubicin, cyclophosphamide, and etoposide; and vincristine, doxorubicin, and cyclophosphamide. The reader is cautioned that, despite this recommendation, there are no controlled trials testing the effect of postoperative chemotherapy in patients with SCLC-SPN or stage I SCLC.

Radiotherapy

The exact role of radiotherapy in SCLC-SPN is unclear because no studies have specifically addressed this issue. In many studies on stage I SCLC, radiotherapy was not employed in a systematic way; in others, a thoracic dose now considered suboptimal for patients with limited disease was chosen. In two studies, a total of only seven patients with SCLC-SPN received thoracic radiotherapy as primary or adjuvant therapy, and seven patients received prophylactic cranial radiotherapy. These data are insufficient to permit conclusions regarding the survival benefit of such treatment. Until more information is available, we suggest an approach similar to that recommended for patients with limited SCLC, using 5,000 cGy in 200-cGy fractions over five weeks to the mass, the hilum, the mediastinum, and the supraclavicular fossae. In addition, prophylactic cranial irradiation should be administered. This treatment alone may be sufficient adjuvant therapy for those who are unsuitable for, or who refuse, chemotherapy. Others may receive the same regimen in conjunction with four to eight cycles of chemotherapy.

Table 3—Life-Table Survival Estimates for Patients with Surgically Treated Stage I SCLC*

<table>
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<th>Interval, mo</th>
<th>All Stage I†</th>
<th>T1NO</th>
<th>T2NO</th>
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<tr>
<td></td>
<td>N</td>
<td>Survival, %</td>
<td>N</td>
</tr>
<tr>
<td>0-12</td>
<td>310</td>
<td>87</td>
<td>66</td>
</tr>
<tr>
<td>12-24</td>
<td>261</td>
<td>74</td>
<td>58</td>
</tr>
<tr>
<td>24-36</td>
<td>202</td>
<td>61</td>
<td>49</td>
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<tr>
<td>36-48</td>
<td>161</td>
<td>51</td>
<td>40</td>
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<tr>
<td>48-60</td>
<td>96</td>
<td>40</td>
<td>26</td>
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<tr>
<td>60+</td>
<td>73</td>
<td>23</td>
<td>23</td>
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*Data are derived from several studies. N = number of patients alive at start of each interval.
†Includes some patients with older-classification stage I disease (including T1N1).
PROGNOSIS

The prognosis of patients with SCLC-SPN relative to others with limited disease of the same histologic type is unknown. Since this is a rare clinical entity, no studies have adequately compared treatment modalities, and there is insufficient information on the prognostic value of surgery, chemotherapy, radiotherapy, and combinations thereof. Surgically treated patients represent a specially selected subset with lower disease stage, and are likely to have superior performance status and less cardiopulmonary comorbidity than other nonsurgical patients with limited disease. Moreover, the comparison of pathologically staged surgical patients with clinically staged nonsurgical patients would not be valid.

Figure 2 illustrates survival for patients with SCLC-SPN, using data from three published series in which survival of individual patients is recorded.2,11,56 It is important to note that these patients received a variety of treatment regimens, including those listed above. It is of interest that the survival of these patients is similar to that within the broader category of patients with surgically resected stage I SCLC (Fig 1), with a five-year survival of approximately 45 percent. Thus, although it would seem that patients with small peripheral tumors should have a better prognosis than those with proximal lesions, this has not been proved for those with stage I disease.57

The three most important prognostic features in resected SCLC are surgical-pathologic disease stage, histologic subtype, and the use of surgery as treatment. The first two of these have already been discussed in detail.

Although associated with favorable survival, at least in the short term, the prognostic importance of surgery is difficult to evaluate. The results in limited SCLC have not always been consistent. Thus, Davis et al58 found that surgery as initial therapy was the only factor related to two-year survival once stage was accounted for. On the other hand, Osterlind et al38 failed to show a definite advantage for surgery compared with other therapy in a similar group of patients. Discrepancies in surgical series may result from inherent biases, including incomplete staging, patient selection, and the exclusion of patients who refuse surgery or who become ineligible following initial chemotherapy.20 The role of surgery in patients with limited SCLC may be better understood when the results of the Lung Cancer Study Group trial are revealed. In this study, all patients are treated with chemotherapy and then randomized to surgery or no surgery arms only after careful clinical restaging.

CONCLUSIONS

Small cell lung cancer presenting as an SPN is an unusual and unique tumor with features that may distinguish it from typical SCLC. Currently, the recommended treatment is surgery followed by adjuvant chemotherapy and/or radiotherapy. Further studies are required to assess the efficacy of each treatment modality and to predict which therapy or treatment combination is optimal for a given patient. A prospective randomized controlled trial testing the role of surgery for SCLC-SPN, although highly desirable, may not be feasible because this entity is usually diagnosed following resection. Moreover, evaluation of the roles of chemotherapy and radiotherapy will be limited by the rare occurrence of SCLC-SPN and stage I SCLC. Nevertheless, optimism is warranted, since aggressive therapy offers the hope of long-term survival and even cure for patients with this lesion.

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