Modern Staging of Small Cell Lung Cancer

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Abstract

For many years, small cell lung cancer (SCLC) has been staged using the Veterans Affairs classification system, which includes only 2 stages: limited (primary tumor and regional lymph nodes within a tolerable radiation field) and extensive (anything beyond limited stage). The TNM staging system used for non–small cell lung cancer is also prognostic for SCLC and should be integrated into the classification scheme for patients with SCLC. The staging workup for SCLC has traditionally included contrast-enhanced CT scans of the chest and abdomen, bone scan, and MRI or CT scan of the brain. Recent data suggest that PET can improve both staging accuracy and treatment planning in patients with SCLC, although further prospective studies are needed to fully define its role. (*JNCCN* 2013;11:99–104)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the TNM staging system for the classification of patients with SCLC.
- Describe the optimal staging work-up for patients with SCLC.

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Small cell lung cancer (SCLC) is characterized by neuroendocrine differentiation, early metastatic spread, and initial responsiveness to cytotoxic therapy. Its overall incidence and proportional incidence as a percentage of all lung cancer cases have been declining over the past 2 decades, with SCLC now accounting for approximately 15% of all lung cancer cases.[1] Although limited-stage SCLC is potentially curable, most patients present with more advanced disease, and the overall survival of patients with SCLC remains poor. Accurate staging is a critical aspect of patient management because it not only provides important prognostic information but also determines appropriate treatment strategies.

Staging Systems

The Veterans Administration Lung Study Group (VALSG) 2-stage classification scheme has been routinely used for the clinical staging of SCLC for at least 40 years.[2] The original VALSG system defined limited-stage as: 1) disease confined to 1 hemithorax, although local extension may be present; 2) no extrathoracic metastases, except for ipsilateral supraclavicular lymph nodes if they can be included in the same radiation port as the primary tumor; and 3) primary tumor and regional nodes that can be adequately encompassed in a radiation port. Extensive-stage was defined as disease that cannot be classified as limited, including malignant pleural or pericardial effusions, contralateral hilar or supraclavicular lymph nodes, and hematogenous metastases. In 1989, the International Association for the Study of Lung Cancer (IASLC) proposed a modification to the VALSG system in which limited-stage SCLC was expanded to include contralateral mediastinal or supraclavicular lymph node metastases and ipsilateral pleural effusions independent of cytology.[3] Extensive-stage SCLC remained any disease at sites beyond the definition of limited disease. A single-institution retrospective review of 109 patients with SCLC suggested that the IASLC staging system had better prognostic discrimination than the VALSG scheme.[4] In practice, most clinicians and clinical trials blend the VALSG and IASLC criteria by classifying contralateral mediastinal and ipsilateral supraclavicular lymph node involvement as limited-stage. The classification of contralateral supraclavicular or hilar lymph node involvement remains controversial, with treatment usually determined individually based on the ability to include these regions in a tolerable radiotherapy port.

The use of a simplified 2-stage system is based on both the biologic characteristics of SCLC and the available therapeutic options. Most patients present with extensive-stage disease for which systemic chemotherapy is the standard treatment. All patients with limited-stage disease, regardless of the visible extent of tumor, also receive systemic chemotherapy because of the high probability of micrometastatic disease and the high initial responsiveness to cytotoxic therapy. Because all patients with SCLC will receive platinum-based chemotherapy regardless of stage, the primary stage-dependent clinical management decision is whether a local therapeutic modality (ie, radiotherapy or surgery) should be added to systemic therapy. A local modality is included in initial therapy only in patients without distant metastases (ie, patients with limited stage disease). Surgery is rarely used for treating SCLC because nearly all patients with limited-stage SCLC have bulky mediastinal lymph node involvement that is not amenable to definitive surgical resection. Therefore, the 2-stage system has worked well to define initial treatment for most patients with SCLC: chemotherapy for extensive-stage and chemoradiotherapy for limited-stage.

Recently, the IASLC proposed that the newly revised TNM staging classification for lung cancer[5] (staging table available online, in the NCCN Guidelines for SCLC, at NCCN.org [ST-1]) should replace the VALSG system for SCLC. This recommendation is based on a prognostic analysis of 8088 patients diagnosed with SCLC between 1990 and 2000 who were included in the IASLC database and had adequate data to determine clinical (c) or pathologic (p) TNM stage.[6,7] In clinically staged patients without hematogenous metastases, both the cT and cN descriptors were discriminatory for overall survival (both $P<.0001$).[6] However, no significant survival difference was seen between the cN0 and cN1 subsets.[6] The overall clinical stage I–IV groupings were also predictive of overall survival, and this finding was validated in a cohort of 4884 patients with SCLC from the SEER registry.[6] However, cT stage seemed to be a more important prognostic predictor than cN stage, because the survival curves overlapped for patients with stages IA and IIA disease and those with IB and IIB disease.[6] The survival rates

of patients with pleural effusions but otherwise limited-stage disease were intermediate between those of patients with limited-stage disease without effusion and patients with extensive-stage disease, regardless of pleural fluid cytology. Data were insufficient to determine the prognostic impact of contralateral supraclavicular lymph node involvement compared with ipsilateral supraclavicular or contralateral mediastinal lymph node involvement.

A separate analysis of 349 patients in the IASLC database with SCLC pathologically staged by complete (R0) resection also showed the prognostic impact of the pT and pN classifiers.[7] Using the newer TNM system, the pathologic stage I–IV groupings also correlated with overall survival, although only the differences between stages IIB versus IIIA and IIIA versus IIIB achieved statistical significance.[7] An independent analysis of 10,660 patients with SCLC from the California Cancer Registry also confirmed the prognostic value of the T and N classifiers and the overall stage I–IV groupings.[8]

These retrospective studies support the applicability of the new TNM staging scheme to SCLC. However, the degree of prognostic discrimination with the TNM system seems less impressive for SCLC than for non–small cell lung cancer.[5] In addition, because most clinical trials in SCLC have used the VALSG staging system, the application of TNM staging is unlikely to significantly alter clinical decision-making. Nevertheless, TNM staging does have utility in selecting patients for surgical resection (ie, those with T1–2,N0 disease). TNM staging may also allow for improved consistency in radiation treatment planning, given the recent trend toward involved-field rather than elective nodal radiation for the treatment of limited-stage SCLC. As a rule, TNM staging should be implemented in clinical trial stratification and tumor registry accession to allow future refinement of appropriate therapeutic options.

Staging Workup

The standard initial evaluation of patients with newly diagnosed SCLC consists of a complete medical history and physical examination, pathologic review of biopsy specimens, and laboratory studies. Because limited-stage SCLC is a potentially curable disease, the most important part of staging is screening for distant hematogenous metastases. Although SCLC can metastasize almost anywhere in the body, the most common sites are the lungs, pleura, bones, adrenal glands, liver, and brain. Standard procedures to identify metastatic disease include contrast-enhanced CT scans of the chest and abdomen, bone scan, and MRI or CT scan of the brain. Brain imaging should be obtained in all patients with SCLC, because MRI scans will detect metastatic disease in 10% to 15% of neurologically asymptomatic patients at initial diagnosis, including 12% of patients with otherwise limited-stage SCLC.[9,10] Bone marrow aspiration and biopsy can detect metastatic SCLC cells in 15% to 30% of patients at diagnosis.[11–13] However, fewer than 5% of patients will have bone marrow involvement as the only site of metastatic disease.[11–13] Therefore, routine bone marrow examination is not indicated in patients with SCLC with normal blood counts. Recently, PET has been incorporated into the SCLC staging workup in conjunction with diagnostic CT scans of the chest and abdomen and brain imaging with MRI or CT.[14]

PET in SCLC

The utility of PET in the initial staging of patients with SCLC was evaluated in 14 studies comparing pretreatment ^{18}F-fluorodeoxyglucose (FDG)-PET with conventional staging procedures[15–28] (Table 1). Each of these studies has been small (range, 7–120 patients), comprising a total of 478 patients, and only 5 studies were prospectively designed (n=209).[18,20,21,23,24] Study designs varied regarding the specific conventional staging procedures, the use of PET alone or PET/CT, and the methods used to define PET positivity. In addition, some studies required biopsy of all FDG-avid lesions that would alter stage, whereas others used clinical or further imaging follow-up to confirm PET findings. Unfortunately, several studies did not validate PET findings using any other method.

Because of the high metabolic activity of SCLC, the sensitivity of PET for the detection of primary tumors is 100%.[15–17,20,21,23,28] Overall, cumulative staging concordance between PET and conventional imaging was 84%,[15–28] with better concordance in the prospective (89%; range, 83%–100%) than the retrospective (81%; range, 50%–100%) studies. Of the 274 patients with limited-stage SCLC according to conventional imaging, 18% were upstaged to extensive stage based on PET results, with similar findings in the prospective (17%; range, 0%–33%) and

Table 1 PET for Initial Staging of Small Cell Lung Cancer

Trial	N	Stage Concordance	LS n	LS Upstaged (LS→ES)	ES n	ES Downstaged (ES→LS)
Prospective						
Chin et al.[18]	18	83%	9	22%	9	11%
Bradley et al.[20]	24	88%	24	8%	_	_
Brink et al.[21]	120	88%	51	20%	69	4%
Kut et al.[23]	18	100%	6	0	12	0
Fischer et al.[24]	29	83%	9	33%	20	5%
Subtotal	**209**	**89%**	**99**	**17%**	**110**	**5%**
Retrospective						
Hauber et al.[15]	7	100%	6	0	1	0
Schumacher et al.[16]	26	73%	13	54%	13	0
Shen et al.[17]	25	92%	10	10%	15	7%
Kamel et al.[19]	24	83%	17	18%	7	14%
Blum et al.[22]	15	67%	15	33%	–	–
Niho et al.[25]	63	92%	63	8%	–	–
Vinjamuri et al.[26]	51	82%	18	6%	33	18%
Azad et al.[27]	46	74%	26	15%	20	40%
Arslan et al.[28]	12	50%	7	71%	5	20%
Subtotal	**269**	**81%**	**175**	**18%**	**94**	**18%**
Total	**478**	**84%**	**274**	**18%**	**204**	**11%**

Abbreviations: ES, extensive stage; LS, limited stage.

retrospective (18%; range, 0%–71%) studies.[15–28] Of the 204 patients with extensive-stage SCLC on conventional imaging, 11% were downstaged to limited stage based on PET results, with a much lower percentage of downstaged patients noted in the prospective (5%; range, 0%–11%) than retrospective (18%; range, 0%–40%) studies.[15–19,21,23,24,26–28] PET was superior to standard imaging in both sensitivity and specificity at most metastatic sites of disease.[15–17,20,21] However, PET was inferior to MRI or CT for the detection of brain metastases.[21,26]

Seven studies have evaluated changes in initial management based on PET in patients with SCLC (Table 2).[19,20,22,23,27,29,30] Overall, PET findings led to a change in initial management in 28% (range, 0%–47%) of 211 patients. Of the 59 patients with a change in management, 32% underwent an alteration in the general treatment plan as a result of stage shift, whereas 68% had changes in the extent of the radiation field for the treatment of limited-stage SCLC. In one of these studies, only 3% of patients who underwent PET-guided radiation planning had isolated nodal failure, compared with 11% of historical controls who underwent CT-guided radiation planning, suggesting that the incorporation of PET into radiation planning improved regional disease control.[30]

Only 4 studies, all retrospective, have assessed the use of PET in restaging of SCLC after initial therapy.[16,19,22,28] Major differences in the analytic methods of these studies makes it difficult to generalize findings, but overall 20% to 57% of patients were found to have more disease and 14% to 38% less disease based on PET results compared with traditional CT restaging alone.[16,19,22,28]

Overall, the use of PET, in addition to CT scans of the chest and abdomen and MRI or CT of the brain, seems to improve the accuracy of initial staging and radiotherapy planning in patients with SCLC. If PET is obtained for initial staging, pathologic confirmation is required for findings that result in staging changes that would affect clinical management. However, further well-designed prospective trials with pathologic confirmation of imaging

Table 2 Change in Initial Management Based on PET Findings

Trial	N	Change in Management	Change in RT Field (n=190)	Change in Treatment (n=130)
Prospective				
Bradley et al.[20]	24	33%	29%	4%
Kut et al.[23]	21	0	NR	0
von Loon et al.[30]	60	30%	30%	NR
Retrospective				
Kamel et al.[19]	24	37%	21%	17%
Blum et al.[22]	15	47%	13%	33%
Azad et al.[27]	46	26%	7%	20%
von Loon et al.[29]	21	24%	24%	NR
Total	**211**	**28%**	**21%**	**15%**

Abbreviations: NR, not reported; RT, radiotherapy.

findings are still needed to fully determine if the addition of PET to conventional staging procedures has a favorable impact on overall clinical outcome in patients with SCLC.

Conclusions

Although SCLC remains an overwhelmingly devastating disease, advances in staging technology have allowed practitioners to better focus aggressive treatments on patients who will most benefit. The emergence of PET may allow further discrimination between potentially curable patients with limited-stage SCLC and those with extensive-stage SCLC for whom palliative treatment remains the only option. Although the 2-stage VALSG staging criteria have provided adequate classification for many years, the time has come to integrate the TNM system into the evaluation of patients with SCLC. As therapy improves over time, the finer parsing of disease extent provided by TNM staging will hopefully allow practitioners to better define more specific and appropriate individualized treatments for patients with SCLC.

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Posttest Questions

1. Small cell lung cancer (SCLC) is characterized by:
   a. Neuroendocrine differentiation
   b. Early metastatic spread
   c. Initial responsiveness to cytotoxic therapy
   d. All of the above
2. True or False: Most patients with SCLC present with extensive-stage disease, for which surgery is the standard treatment.
3. Standard procedures to identify metastatic disease include:
   a. Contrast-enhanced CT scans of the chest and abdomen
   b. Bone scan
   c. MRI or CT scan of the brain
   d. All of the above