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REVIEW

Staging and imaging of small cell lung cancer

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Abstract

Small cell lung cancer (SCLC) has been primarily classified as limited or extensive, with limited stage confined to the primary tumor and regional lymph nodes. In the future, the TNM staging system should be integrated into the classification of SCLC. The appropriate staging work-up for patients with SCLC has traditionally included contrast-enhanced computed tomography (CT) scans of the chest and abdomen, bone scan, and magnetic resonance imaging or CT scan of the brain. Recent data suggest that positron emission tomography can improve both staging accuracy and treatment planning in patients with SCLC. Treatment for limited-stage SCLC consists of chemotherapy plus radiotherapy, and such therapy can cure 20–25% of patients. Extensive-stage SCLC is incurable, but chemotherapy can improve quality of life and prolong life.

Keywords: *Small cell lung cancer; staging; positron emission tomography; chemotherapy; radiotherapy.*

Introduction

Small cell lung cancer (SCLC) is a distinct clinicopathologic entity characterized by neuroendocrine differentiation, early metastatic spread, and initial responsiveness to cytotoxic therapy. In the United States, both the overall incidence and the proportional incidence of SCLC as a percentage of all lung cancer cases have been declining over the past 2 decades. The incidence rate of SCLC peaked in the late 1980s and has been declining since then[1,2]. The male-to-female incidence ratio has also fallen dramatically, from 2.6/1 in 1973 to 1/1 in 2002, primarily due to a marked decline in incidence in men coupled with a steady rise in incidence in women[2]. In the late 1980s, the proportional incidence of SCLC peaked at 17–20% of all lung cancer cases, but by 2002, SCLC accounted for only 13–15% of all cases[1,2].

Staging systems

The Veterans' Administration Lung Study Group (VALSG) two-stage classification scheme has been routinely used for the clinical staging of SCLC since the late 1950s[3]. The VALSG system defines limited-stage (LS) as: (a) disease confined to one hemithorax, although local extension may be present; (b) no extrathoracic metastases except for ipsilateral supraclavicular lymph nodes if they can be included in the same radiation port as the primary tumor; and (c) primary tumor and regional nodes that can be adequately encompassed in a radiation port. Extensive-stage (ES) disease is 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 of the VALSG system in which LS-SCLC was expanded to include contralateral mediastinal or supraclavicular lymph node metastases and ipsilateral pleural effusions independent of cytology[4]. ES-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[5]. In practice, most clinicians and clinical trials blend the VALSG and IASLC criteria by considering contralateral mediastinal and ipsilateral supraclavicular lymph node involvement to be LS. 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 safe radiotherapy port.

Recently, the IASLC has proposed that the newly revised TNM staging classification for lung cancer (American Joint Committee on Cancer (AJCC) 7th edition)[6] should replace the VALSG system for the staging of SCLC. This recommendation is based on a prognostic analysis of 8088 patients with SCLC in the IASLC database with adequate data to determine clinical (c) or pathologic (p) TNM stage[7,8]. In clinically staged patients without hematogenous metastases, both the cT and cN descriptors were discriminatory for overall survival (both $P < 0.0001$), although there was no significant difference between cN0 and cN1[7]. The overall clinical stage I–IV groupings were also predictive of overall survival and this finding was validated in a cohort of 4884 SCLC patients from the Surveillance, Epidemiology, and End-Results (SEER) registry[7]. However, cT stage appeared to be more important than cN stage, since patients with stages IA and IIA had similar survival rates, as did those with IB and IIB disease[7]. Interestingly, the survival rates of patients with pleural effusions, but otherwise LS disease, were intermediate between those of LS patients without effusion and ES patients, regardless of pleural fluid cytology. There were insufficient data 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 demonstrated the prognostic impact of the pT and pN classifiers[8]. Using the AJCC 7th edition 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[8]. Independently, an analysis of 10,660 SCLC patients from the California Cancer Registry confirmed the prognostic value of the T and N classifiers, as well as the overall stage I–IV groupings[9].

These retrospective studies support the applicability of TNM staging to SCLC. However, the degree of prognostic discrimination with the TNM system appears less impressive in SCLC than in NSCLC[6]. In addition, since most clinical trials in SCLC have utilized the VALSG staging system, it is unlikely that the application of TNM staging would significantly alter clinical decision making. Nevertheless, TNM staging does have utility in the selection of patients for surgical resection (i.e. those with T1–2 N0 disease). In addition, TNM staging should be implemented in clinical trial stratification and in tumor registry accession in order to allow future refinement of appropriate therapeutic options (Table 1).

Staging work-up

Initial evaluation of patients with newly diagnosed SCLC consists of a complete medical history and physical examination, pathologic review of relevant biopsy specimens, and laboratory studies. Since LS-SCLC is a curable disease, the most important issue in staging is to determine whether or not there are any distant metastases. Traditional standard procedures to identify metastatic disease include contrast-enhanced computed tomography (CT) scans of the chest and abdomen, bone scan, and magnetic resonance imaging (MRI) or CT scan of the brain. MRI scans will detect brain metastases in 10–15% of neurologically asymptomatic patients with SCLC at initial diagnosis, including 12% of patients with otherwise LS-SCLC[10,11]. Bone marrow aspiration and biopsy can detect metastatic SCLC cells in 15–30% of patients at diagnosis[12–14]. However, less than 5% of patients will have bone marrow involvement as the only site of metastatic disease[12–14]. Therefore, routine bone marrow examination is not indicated in patients with SCLC. Recently, positron emission tomography (PET) has been incorporated into the staging evaluation of SCLC in conjunction with diagnostic CT scans of the chest and abdomen and MRI or CT of the brain[15].

PET in SCLC

The utility of PET in the initial staging of patients with SCLC has been evaluated in 12 studies comparing pretreatment [^{18}F]fluorodeoxyglucose (FDG)-PET to conventional staging procedures[16–27] (Table 2). These studies have been relatively small (range, 7–120 patients), comprising a total of 403 patients. Five studies were prospective ($n = 209$)[19,21,22,24,25] and 7 were retrospective ($n = 194$)[16–18,20,23,26,27]. Study designs varied with regard to the extent of conventional staging, the use of PET alone or PET/CT, and the method used to define PET positivity. In addition, some studies required biopsy of all FDG-avid lesions that would alter stage, whereas others used clinical follow-up to confirm PET findings. Unfortunately, several studies did not validate PET findings and stage alterations by either method.

SCLC is a highly metabolic malignancy, leading to a sensitivity of 100% for PET detection of primary tumors[16–18,21,22,24]. Overall, cumulative staging concordance was 84% between PET and conventional imaging[16–27] with better concordance noted in the prospective (89%, range 83–100%) than the retrospective (80%, range 67–100%) studies. Of the 204 patients with LS-SCLC by conventional imaging, 19% were up-staged to ES by PET, with similar findings in the prospective (17%, range 0–33%)) and retrospective (20%, range 0–54%) studies[16–27]. Of the 199 patients with ES-SCLC by conventional imaging, 11% were down-staged to LS by PET, with a much lower percentage of down-staged patients noted in the prospective (5%,

Table 1 Lung cancer TNM staging system (adapted from ref.[6])

Primary tumor (T)	
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (for example, not in the main bronchus)
T1a	Tumor ≤ 2 cm in greatest dimension
T1b	Tumor > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumor > 3 cm but ≤ 7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤ 5 cm): involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor > 3 cm but ≤ 5 cm in greatest dimension
T2b	Tumor > 5 cm but ≤ 7 cm in greatest dimension
T3	Tumor > 7 cm or one that directly invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural (or pericardial) effusion
M1b	Distant metastasis (in extrathoracic organs)

	T	N	M
Anatomic stage			
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

Table 2 PET for initial staging of SCLC

Trial	*N*	Stage concordance (%)	LS		ES	
			N	Up-staged (LS→ES) (%)	*N*	Down-staged (ES→LS) (%)
Prospective						
Chin[19]	18	83	9	22	9	11
Bradley[21]	24	88	24	8	0	–
Brink[22]	120	88	51	20	69	4
Kut[24]	18	100	6	0	12	0
Fischer[25]	29	83	9	33	20	5
Subtotal	209	89	99	17	110	5
Retrospective						
Haubner[16]	7	100	6	0	1	0
Schumacher[17]	26	73	13	54	13	0
Shen[18]	25	92	10	10	15	7
Kamel[20]	24	83	17	18	7	14
Blum[23]	15	67	15	33	0	–
Vinjamuri[26]	51	82	18	6	33	18
Azad[27]	46	74	26	15	20	40
Subtotal	194	80	105	20	89	18
Total	403	84	204	19	199	11

Table 3 Change in management based on PET findings

Trial	*N*	Change in management (%)	Change in radiotherapy field (%)	Change in treatment (%)
Initial PET				
Prospective				
Bradley[21]	24	33	29	4
Kut[24]	21	0	NR	0
Retrospective				
Kamel[20]	24	37	21	17
Blum[23]	15	47	13	33
Azad[27]	46	26	7	20
von Loon[28]	21	24	24	NR
Subtotal	151	27	17	15
Re-staging PET				
Retrospective				
Kamel[20]	20	15	–	15
Blum[23]	25	40	–	40
Subtotal	45	29	–	29
Total	196	28	17	16

range 0–11%) than retrospective (18%, range 0–40%) studies[16–27]. For most metastatic sites, PET was superior to standard imaging in both sensitivity and specificity[16–18,21,22]. However, PET was inferior to MRI or CT for the detection of brain metastases[22–26].

Six studies, 2 prospective[21,24] and 4 retrospective[20,23,27,28], have evaluated changes in management based on PET in patients with SCLC (Table 3). Overall, PET findings led to a change in initial management in 27% (range 0–47%) of the 151 patients included in these studies. Half of these were due to alterations in the general treatment plan due to stage shift; the other half were due to changes in the radiation field in patients with LS-SCLC. Only 3 studies, all retrospective, have assessed the use of PET in re-staging of SCLC after initial therapy[17,20,23]. Lack of uniform data analysis makes it impossible to compile study findings, but in general, 20–25% of patients were found to have more disease and 23–38% less disease by PET compared with traditional CT re-staging alone[17,20,23], and 29% of patients had a change in management based on PET findings[20,23].

The prognostic value of PET in SCLC has been evaluated in 4 studies[23,29–31]. One prospective study of 76 patients with both LS- and ES-SCLC reported a significant association between pre-treatment FDG-uptake level and both progression-free and overall survival, with higher uptake values correlating with poorer prognosis[29]. One potential explanation of this finding is that higher metabolic activity (i.e. FDG uptake) may be a marker for tumors with higher proliferative rates and more aggressive behavior. Three retrospective studies comprising 93 patients demonstrated that patients with a complete response on post-treatment PET had significantly better progression-free and overall survival[23,30,31]. Data regarding the utility of PET to gauge response to therapy in patients with SCLC is sparse.

Overall, the use of PET, in addition to CT scans of the chest and abdomen and MRI or CT of the brain, appears to improve the accuracy of initial staging and radiotherapy planning in patients with SCLC. However, further well-designed prospective trials with pathologic confirmation of imaging findings are still needed to fully define the role of PET in this setting. If PET is obtained for initial staging, pathologic confirmation is required for lesions that result in up-staging. At present, data regarding the potential role of PET in re-staging, response evaluation or prognostic prediction in patients with SCLC are insufficient and inconclusive.

Management OF SCLC

LS-SCLC is a curable disease in which progress has mainly been made through the incorporation of radiotherapy into the standard treatment regimen. In 2 meta-analyses, the addition of definitive thoracic radiation to chemotherapy was found to significantly improve overall survival in patients with LS-SCLC[32,33]. Subsequent studies demonstrated that early thoracic radiotherapy (initiated within the first 2 cycles of chemotherapy) afforded further overall survival benefit when compared with late radiotherapy[34]. Although a large randomized trial has demonstrated an added survival gain with hyperfractionated (twice a day) thoracic radiotherapy, this strategy remains controversial and confirmatory trials are ongoing[35]. During the course of their illness, 50–60% of patients with SCLC develop brain metastases[36]. A meta-analysis of randomized trials evaluating prophylactic cranial irradiation (PCI) reported a 25% absolute decrease in the incidence of brain metastases and a 5.4% increase in 3-year overall survival

($P = 0.01$)[36]. At present, the standard-of-care for the treatment of patients with LS-SCLC consists of 4–6 cycles of cisplatin and etoposide along with early, concurrent thoracic radiotherapy. PCI should be strongly considered for those achieving a good response to initial therapy. With such treatment, 90% of patients with LS-SCLC will have a dramatic response and 20–25% will achieve long-term survival.

For patients with ES-SCLC, the cornerstone of treatment involves platinum-based, 2-drug chemotherapy regimens, such as cisplatin or carboplatin plus etoposide, with the goal of palliating symptoms and prolonging survival. With such treatment, 60–70% of patients will demonstrate substantial response and up to 10% will have a complete radiographic response. After initial chemotherapy, patients who attain a good response and have good performance status should be strongly considered for PCI based on the demonstration of improved survival even in patients with ES disease[37]. Although chemotherapy does significantly improve quality of life and prolong survival for patients with ES-SCLC, relapse is inevitable and only 5% of patients remain alive 2 years after diagnosis. At present, ES-SCLC remains an incurable disease. Numerous chemotherapy-based strategies, including dose intensification, weekly administration, 3- or 4-drug regimens, high-dose consolidation, alternating or sequential non-cross-resistant regimens, and maintenance therapy, have failed to yield convincing improvements in survival, and several of these approaches have resulted in unacceptable toxicity[38].

Over the past 30 years, our knowledge of the biology of SCLC has greatly expanded and preclinical studies have identified many molecular targets for which therapeutic agents have been developed. Many of these rational novel strategies have been evaluated in phase II and III clinical trials in patients with SCLC, but thus far none of them have demonstrated promising clinical activity[39]. Nevertheless, future advances in SCLC will rely on ongoing efforts to refine imaging strategies and to identify the molecular targets that drive survival, proliferation and metastasis.

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