Editorial

Pathological upstaging and treatment strategy of clinical stage I small cell lung cancer following surgery

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Overview

Small cell lung cancer (SCLC) represents approximately 10–15% of all lung cancers, and its incidence has been steadily decreasing in the past two decades, primarily because of reduction in cigarette smoking, which is the primary cause of this type of tumor (1). SCLC originates from neuroendocrine cell precursors and is characterized by rapid growth, early dissemination to regional lymph nodes, and distant metastasis, and resultant poor prognosis along with initial sensitivity to chemotherapy and radiotherapy (2,3). Current standard therapy for SCLC relies on chemotherapy or chemoradiotherapy, even for patients with "limited" disease. In contrast, the role of primary surgical resection in such patients remains controversial because only a minority of early stage SCLC patients presents without metastasis and are candidates for surgery. Recently, based on favorable surgical results reported in several large cohort studies for limited disease SCLC (4-7), the American College of Chest Physicians (ACCP) indicate surgical has recommended resection only for patients with clinical stage I SCLC (T1–2, N0), followed by chemotherapy (8). Similarly, the National Comprehensive Cancer Network (NCCN) guidelines recommend surgery with adjuvant chemotherapy for stage I disease alone and specify lobectomy as the preferred resection procedure (9).

Accurate staging provides prognostic information, which aids in the planning of treatment strategies for all types of lung cancer: non-small cell lung cancer (NSCLC) and SCLC. Use of tumor-node-metastasis (TNM) descriptors has been the basis of the NSCLC staging system since 1973 (10), but these descriptors are seldom used in SCLC staging. Because these systems have historically relied on surgical confirmation for their accuracy, and as stage earlier, patients with SCLC seldom present at a stage for which surgery is appropriate. Instead, most clinicians have used two group staging systems for SCLC, which define the limited stage as tumor being confined to one hemithorax with regional lymph node metastasis including both ipsilateral and contralateral hilar, supraclavicular, and mediastinal nodes, as well as ipsilateral pleural effusion, and these definitions are still most relevant for clinical decision making (11).

More recent studies and the NCCN guidelines use the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis staging for more precise stratification of disease extent. Moreover, the International Association for the Study of Lung Cancer (IASLC) recommendations for SCLC staging notes the significance of T and N stage on survival (12). The current lung cancer TNM staging system was developed by IASLC and adopted by the AJCC Cancer Staging Manual 7th edition; this staging system is applicable to both NSCLC and SCLC based on studies by the IASLC that showed the prognostic significance of various stage designations in both diseases (4,12-14). The current TNM staging system is based on 8,088 SCLC patients and provides better prognostic information and more precise

nodal staging, which is required for conformal radiation techniques and intensity-modulated radiation therapy. The former term "limited stage" would now include T1–4, N0–3, and M0 tumors, whereas metastatic tumors encompass former extensive-stage patients. In addition, T1/T2 N0/N1 M0 tumors, previously described as "very limited stage" tumors, were identified as a group with more favorable outcomes compared with patients with N2/N3 tumors, which must be considered for curative-intent surgery according to expert consensus.

Upstaging

Clinical staging is often applied in order to guide management and pathological staging to predict prognosis, although the two aims are often not mutually exclusive. Approximately 5% of patients with SCLC present with T1/2 N0/1 M0 tumors; such patients have more favorable outcomes with 5-year survival rates of approximately 50% (6,15); moreover, surgical approaches are justified in such patients after ruling out mediastinal lymph node involvement. Despite advances in the diagnosis and preoperative staging of lung cancer using positron emission tomography-computed tomography (PET-CT) (16), pathological upstaging of early-stage disease remains a common finding (17,18). A recent review suggested that with PET-CT, 9% of patients are upstaged whereas 4% are downstaged; thus, PET-CT findings that could affect treatment decisions should be pathologically confirmed (19). The current staging protocols may underestimate the disease extent in up to 28% of patients with clinical stage I NSCLC (20,21). On the other hand, the overall concordance between clinical and pathological TNM staging was 58% in IASLC data bases of SCLC (4). Before curative-intent surgery, invasive mediastinal staging such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) (22) and surgical mediastinoscopy (8) is recommended to evaluate for regional and distant disease conditions, particularly for SCLC, because nodal involvement designation has traditionally been considered as a contraindication to surgery. Therefore, the present manuscript must be meaningful, as well as previous studies, and one of the largest nationally representative data pool that could identify the incidence of pathological upstaging (19.7–25%) after surgical resection of SCLC (*Table 1*).

Treatment modality

Despite changes in demographics and treatment, the median and 5-year survival rates for patients with SCLC have not improved remarkably over the past 15 years. Based on analysis of 68,611 patients with SCLC in NCDB, the median survival of patients with ESCLC and LSCLC was 6.1 and 12.9 months in 2007, respectively, which did not improve markedly from the median survival reported between 1992 and 2002 (25). Nevertheless, in small surgical series of patients with SCLC, the TNM staging system has been prognostic of outcomes, particularly in the era of adjuvant chemotherapy. The average 5-year survival reported in this large series of stage I SCLC after resection is 52%, which is in line with the corresponding values reported in current large-scale studies (*Table 1*) (4,6,7,23). Based on analysis of these databases, surgery seems to offer reasonable survival in patients who are node negative and undergo lobectomy.

Data regarding clinical outcomes of patients who are pathologically upstaged because of nodal metastases is limited, which is critical to define postoperative recommendations for adjuvant therapy. Moreover, in patients with nodal disease identified at the time of surgical resection, recommendations for the use of adjuvant radiation therapy in addition to chemotherapy are based upon limited evidence. Nevertheless, additional chemoradiotherapy seems reasonable for patients with nodal disease identified at the time of surgical resection as well as those with LSCLC, for which chemoradiotherapy is the standard treatment. Although such patients should receive four cycles of adjuvant chemotherapy and postoperative thoracic radiotherapy when staged pN1 or pN2 in the present manuscript, no improvement in survival has been observed in such patients according to analyses of other large national data bases (*Table 1*).

Guidelines for treatment of patients with pathological nodal disease after surgery are based on limited evidence. Several studies have investigated the role of surgery combined with chemotherapy and radiation therapy to improve local recurrence rates but have reported mixed results (26-28). In contrast, patients with limited disease can be successfully treated with combined concomitant chemoradiotherapy, known to provide a cure rate of 15–20% (29) but a local recurrence rate of as high as 50% (30). Therefore, NCCN and European Society for Medical Oncology (ESMO) guidelines recommend adjuvant chemotherapy and radiation therapy for patients found

Table 1 National database analysis of surgical cases of SCLC by the 7th TNM classification

Authors and journal	Database	Year	N	c-stage (%)	p-stage (%)	5-year survival range (%)	Comments
Vallières *et al.*, *J Thorac Oncol* [2009] (4)	IASLC	1990–2000	349	IA =34%; IB =25%; IIA =4%; IIB =9%; IIIA =21%; IIIB =5%; IV =2%	IA =22%; IB =22%; IIA =12%; IIB =9%; IIIA =21%; IIIB =11%; IV =3%	pIA =56%; pIB =57%; pIIA =38%; pIIB =40%; pIIIA =12%; pIIIB =0%	19.7% of cI–II upstaged to pIIIA; NA regarding to adjuvant therapy
Yu *et al.*, *J Thorac Oncol* [2010] (6)	SEER	1988–2004	1,560	ND	I =100%	LB with RT =57.1%; LB without RT =49.1%; P=0.90	No CT data on SEER
Weksler *et al.*, *Ann Thorac Surg* [2012] (7)	SEER	1988–2004	895	I =76%; II =24%	ND	34 months of MST; Survival advantage of surgery in cI–II	No survival improvement in addition of RT
Takei *et al.*, *J Thorac Oncol* [2014] (23)	JLCR	2004	243	IA =54.3%; IB =14.3%; IIA =10.3%; IIB =4.1%; IIIA =12.3%; IIIB =1.2%; IV=2.9%	IA =38.3%; IB =21.0%; IIA =11.1%; IIB =7.0%; IIIA =18.5%; IIIB =0.4%; IV =3.7%	pIA =72.3%; pIB =61.1%; pIIA =44.8%; pIIB =40.3%; pIIIA =23.4%; pIV =0%	23.2% of cIAB upstaged p-stage II or III. No survival improvement in addition of adjuvant CT
Thomas *et al.*, *Lung Cancer* [2017] (24)	NCDB	2004–2013	477	IA =84.2%; IB =16.8%		Same stage =52%; upstage =36%; P<0.01	25% of cIAB upstaged p-stage II or III. Survival improvement of additional CT/RT in upstage cases

IASLC, International Association for the Study of Lung Cancer; SEER, Surveillance Epidemiology and End Results; JLCR, Japanese Lung Cancer Registry; LB, lobectomy; RT, radiation; CT, chemotherapy; ND, no data; NA, no analysis.

to have nodal disease (pN+) following curative resection; however, both groups cite these recommendations based on insufficient or lower level of evidence (9,31).

Limitations

Limitations of this analysis include a retrospective study, no randomization for adjuvant treatment, lack of preoperative histopathological diagnosis data, lack of information regarding preoperative staging methods, no information regarding aims of preoperative treatment and whether induction treatment was followed by surgery or salvage surgery. Selection bias in selecting patients who should or should not receive radiation therapy remains unknown. Finally, there was no central pathology review. It must be emphasized that "resectable" SCLC represents only a small proportion of patients with SCLC, which tends to magnify the effects of selection.

Conclusions

Indications for surgical resection of SCLC have been extremely limited. Because "resectable" SCLC represents only a small proportion of patients with SCLC, studies comparing surgical resection among a large number of patients are unlikely to be conducted. This study presents data on >1,000 patients with clinical stage I SCLC who underwent resection, indicating the national practice patterns and outcomes, and thus provides additional insight into the role of surgery in such cases. Based on this analysis, surgery did seem to have a vital role in the management of selected patients with clinical stage I SCLC who revealed favorable survival outcomes. Based on these findings, four cycles of adjuvant chemotherapy should be administered after surgery. On the other hand, postoperative radiotherapy should be considered in cases of unforeseen N2 or N1 or in patients who have not undergone systematic nodal dissection.

Further evaluation of this question is warranted before an actionable recommendation can be made; in fact, additional studies to confirm this are underway. This should be the aim of continued clinical studies, and prospective randomized clinical trials are required to assess the effects of adjuvant chemoradiotherapy after surgery in patients with pathological stage II–III tumors, which may more clearly identify patient and tumor characteristics associated with improved outcomes after primary resection. Additional studies are needed to improve the existing clinical classification models for patients who are potentially suitable for surgery and to develop better prognostic models in patients undergoing complete resection for SCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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