Editorial

Role for adjuvant chemotherapy in patients with resected small cell lung cancer

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Submitted Jun 11, 2016. Accepted for publication Jun 15, 2016.
doi: 10.21037/jtd.2016.07.15
View this article at: http://dx.doi.org/10.21037/jtd.2016.07.15

Lung cancer is the leading cause of cancer-related mortality in the United States (1). Small cell lung cancer (SCLC) accounts for approximately 13% of all patients with lung cancer (2). SCLC has traditionally been staged using the Veterans' Affairs Lung Study Group staging system, which subdivides tumors into limited-stage (LS-SCLC) and extensive-stage (ES-SCLC) based on the presence of tumor confinement into one hemithorax and included in one radiotherapy port (3). More recently, patients with SCLC have been staged using the AJCC system. Although further subdivision of patients with LS-SCLC using the tumor (T) and lymph node (N) status usually does not affect the treatment decision, it has prognostic implications, with significant differences in overall survival (OS) among the TNM subsets for stages I to III (4).

The optimal initial treatment for patients with SCLC and good performance status currently involves the use of a platinum-based chemotherapy regimen for those with ES-SCLC with the addition of concurrent thoracic radiotherapy in LS-SCLC. However, there appears to be a role for surgical resection in LS-SCLC, particularly for patients with very early stage SCLC, defined as stage IA or IB, where it is recommended by the National Comprehensive Cancer Network Guidelines (NCCN) (5). Furthermore, data from several institutions and a National Comprehensive Cancer Database (NCDB) study suggest a role for surgical resection in patients with stages II and III (6,7).

Although there are clear guidelines for the non-surgical treatment of patients with LS-SCLC, there is limited data on adjuvant therapy, particularly for patients with resected stage I disease. In an attempt to investigate the role of adjuvant chemotherapy in this setting, Yang and colleagues evaluated 954 patients with completely resected pathologic stage T1–2N0M0 SCLC between 2003 and 2011 using the NCDB (8). Among the patients undergoing resection, 388 (40.7%) received no adjuvant therapy and 566 (59.3%) received some type of adjuvant therapy including adjuvant chemotherapy in 354 (37.1%), adjuvant chemoradiation in 190 (19.9%) and adjuvant radiation alone in 22 (2.3%) patients. The demographic characteristics were balanced between the two groups of patients, although the adjuvant group had a lower median age (65.8 *vs.* 68.3 years, P<0.01) and higher percentage of private insurance (35.3% *vs.* 27.1%, P<0.04). More importantly however, was the similar distribution of co-morbidity scores, gender, pathologic T status, tumor size and type of resection. The study showed that compared to surgery alone, adjuvant therapy was associated with a significant increase in the median OS from 42.1 to 66.0 months (P<0.01) and 5-year OS from 40.4% to 52.7%. In a multivariable analysis, the highest benefit, compared to surgery alone, was observed in the 99 patients who received adjuvant chemotherapy and brain radiation [hazard ratio (HR), 0.52; 95% confidence interval (CI), 0.36–0.75; P<0.01] and the 354 patients that received chemotherapy alone (HR, 0.78; 95% CI, 0.63–0.95; P=0.02), while there was no significant benefit from chemoradiotherapy to the lung, radiation to the lung or radiation to the brain alone.

Despite the large number of patients, this NCDB study has several limitations including the retrospective nature of the data and the possibility of many confounding variables that were not accounted including the reason for patients not receiving adjuvant chemotherapy, which drugs were administered and how many cycles were used. Since the NCDB records only what the radiation oncologist defines as the most important radiation therapy during the first course of treatment, it is

not clear whether some patients received both intracranial and thoracic radiotherapy. Furthermore, adjuvant treatment defined as chemotherapy given within 5 months after surgery and radiation administered within 8 months after surgery cannot exclude the possibility that some patients were treated for relapsed disease rather than as adjuvant therapy.

Nevertheless, this large NCDB study on resected SCLC patients suggests a benefit from both adjuvant chemotherapy and radiation to the brain, most likely in the form of prophylactic cranial irradiation (PCI). These data are consistent with the biology of SCLC, which is considered a systemic disease at diagnosis even in patients with early stage disease, requiring systemic therapy and brain radiation therapy in an attempt to eradicate micrometastatic disease and increase the probability of cure. Therefore, in the absence of a prospective clinical trial, it seems reasonable to offer adjuvant chemotherapy and PCI for patients with resected stage I SCLC, with the recommendation extending to patients with stages II and III.

Although chemotherapy seems to improve the outcomes for patients with resected stage I SCLC, the NCDB showed a 5-year OS of only 53% in this population presenting with the earliest possible stage for this malignancy. Therefore, novel therapies are required to increase the cure rates for patients treated with surgery or chemoradiotherapy for LS-SCLC. Promising strategies in patients with advanced stage such as immune checkpoint inhibitors alone or in combination and the antibody drug conjugate against delta-like protein 3 (DLL3) rovalpituzumab tesirine may eventually be incorporated in the initial treatment of patients with earlier stage SCLC, including in the adjuvant setting (9,10).

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Lei Deng (West China Hospital, Sichuan University, Chengdu, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Yang CF, Chan DY, Speicher PJ, *et al.* Role of adjuvant therapy in a population-based cohort of patients with early-stage small-cell lung cancer. J Clin Oncol 2016;34:1057-64.

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Cite this article as: Du L, Waqar SN, Morgensztern D. Role for adjuvant chemotherapy in patients with resected small cell lung cancer. J Thorac Dis 2016;8(8):1891-1892. doi: 10.21037/jtd.2016.07.15