Resected small cell lung cancer—what do we do next?

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Submitted Apr 28, 2016. Accepted for publication May 08, 2016.
doi: 10.21037/atm.2016.05.41
View this article at: http://dx.doi.org/10.21037/atm.2016.05.41

Small cell lung cancer (SCLC) accounts for only 15% of lung cancers diagnosed in the United States; however it represents the 5th leading cause of cancer related mortality (1). Cytotoxic chemotherapy, with or without radiation therapy, is the primary modality for the treatment of SCLC as this particular histology is exquisitely chemosensitive with initial response rates around 65% (2). SCLC is typically diagnosed in the more advanced stages of disease. Even in patients with limited stage disease, there is often evidence of mediastinal or nodal involvement by the tumor. Only rarely (<5%) is it discovered as an isolated lung nodule or in a resectable stage (3). However, when it is found as a solitary nodule, surgical resection becomes a therapeutic option. Whether adjuvant therapy adds any benefit has not yet been proven. Dr. Yang *et al.* conducted a retrospective review of 954 patients with T1–2N0M0 SCLC or combined SCLC who underwent R0 surgical resection (4). Patients were identified via the National Cancer Data Base who received treatment between 2003 and 2011. Overall survival (OS) was the primary endpoint and was determined according to whether patients received adjuvant chemotherapy, radiation, or a combination of the two modalities.

The standard treatment for early or limited stage disease involves concurrent chemoradiation therapy given a proven survival benefit over chemotherapy alone (5). The role of surgery in limited stage disease is not well defined. A prior review of the SEER database demonstrated improved survival in patient with early stage SCLC who underwent surgery (6). Five-year survival rates in patients with no nodal disease have been reported as high as 68% with surgical resection (7). A more recent retrospective review found similar results. Survival was improved in stage I patients when they underwent surgical resection as compared to conventional treatment (8). However, data on surgical resection in SCLC is limited and represents a very small minority of the cases reported in large surgical series.

To date, there have been no large, randomized, prospective trials looking at the role of adjuvant therapy in resected SCLC patients, so Yang's cohort analysis provides the most comprehensive view at this juncture. A total of 954 patients were in included in the cohort. It was a very selective patient population, limited to patients with pathologic TNM staging of T1–2N0M0. It is important to recognize that this cohort looked specifically at patients without nodal disease. Surgical resection should mandate appropriate pathologic staging of the mediastinum preoperatively as the concordance between clinical and pathological staging is poor (58%) (3). SCLC has an aggressive biology inherently and has a high rate of distant dissemination even in limited stage disease (9).

This analysis included patients who received adjuvant therapy up to 5 months post operatively. Most trials mandate earlier administration of chemotherapy in the adjuvant setting. The specifics of the chemotherapy administered, the dosing, and the number of cycles was not available in the searched database, although it is reported that 88.4% received multi-agent chemotherapy regimens. Results did demonstrate an improvement in OS when adjuvant chemotherapy was employed with median OS of 66 months with chemotherapy *vs.* 42.1 months without. This database review does not address the best regimen, dosing, or duration.

In limited stage disease, chemotherapy alone results in high rates (75–90%) of local or intrathoracic recurrence and

failure (10). This analysis did not demonstrate any survival benefit when chest radiation was added to the adjuvant regimen; however, the sample size was notably small. Also, the reporting of the type of radiation received was not clearly defined. The database reports only included a single site of radiation; therefore patients may have received both prophylactic cranial irradiation (PCI) and thoracic radiation, but only one of those sites would have been listed. This population also was essentially pathologic N0 disease; therefore these results do not help define the role of chemoradiation in those patients with microscopic nodal disease found post operatively.

Intracranial metastases are a frequent occurrence in SCLC, regardless of depth of tumor response in the thorax. Even patients who achieve a complete response with standard chemoradiation have demonstrated a 45% incidence of central nervous system relapse (11). PCI has resulted in improved survival in patients with limited stage SCLC (12). Consideration of PCI is now the standard recommendation in patients who achieve an initial response to chemoradiation. Dr. Yang's analysis demonstrated improved 5-year survival in patients who received adjuvant chemotherapy and radiation to the brain (presumed PCI) compared with patients who received surgery alone (HR 0.52; P<0.01). Sample sizes were small, but the survival benefit did reach statistical significance. The survival benefit of PCI alone in this specific patient population is unclear and a separate trial evaluating its benefit is warranted.

In summary, despite the inherent drawbacks of a retrospective database analysis, these results indicate a clear benefit for adjuvant chemotherapy following resection of T1–2, N0 SCLC. It is unclear from this analysis what percentage of patients received both chest and brain irradiation, thus the benefits of either are not well defined in this patient population; however, resected, early stage SCLC patients should likely be considered for adjuvant PCI. Despite these results, 5-year survival in this select group of good prognosis patients, who have had optimal therapy, is only 52%. Future studies should evaluate approaches to improve these outcomes.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by Section Editor Jianrong Zhang, MD (Department of Thoracic Surgery, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease, Guangzhou, 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: Marr AS, Ganti AK. Resected small cell lung cancer—what do we do next? Ann Transl Med 2016;4(15):288. doi: 10.21037/atm.2016.05.41

