

Resected small cell lung cancer—time for more?

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Abstract: Small cell lung cancer (SCLC) often presents with either regional or systemic metastases, but approximately 4% of patients present with a solitary pulmonary nodule. Surgical resection can be an option for these patients and is endorsed by the National Comprehensive Cancer Network (NCCN) guidelines. There are no prospective randomized clinical trials evaluating the role of adjuvant systemic therapy in these resected SCLC patients. A recent National Cancer Database analysis found that the receipt of adjuvant chemotherapy alone [hazard ratio (HR), 0.78; 95% CI, 0.63–0.95] or with brain radiation (HR, 0.52; 95% CI, 0.36–0.75) was associated with significantly improved survival as compared to surgery alone. As it is unlikely that a randomized prospective clinical trial addressing this question will be completed, these data should assist with decision making in these patients.

Keywords: Small cell lung cancer (SCLC); surgery; adjuvant chemotherapy; survival

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The incidence of small cell lung cancer (SCLC) in the United States has been decreasing from a peak of 11 per 100,000 person years in the mid-1980s to 7 per 100,000 patient-years in 2010 (1). Although, approximately two thirds of patients with SCLC are diagnosed with advanced disease (2), the remaining patients are diagnosed at a stage where their disease may be curable. However, even in limited stage small cell lung cancer (LS-SCLC), where the goal of therapy is a cure, 5 years overall survival (OS) in clinical trials is only about 25% (3). Thus clearly more needs to be done in order to improve outcomes from this disease.

The mainstay of treatment of LS-SCLC is chemotherapy and radiation (4). However, now emerging data have suggested a role for surgical resection as part of multimodality therapy in LS-SCLC, especially in very early stage disease. A prospective study demonstrated a 5-year survival rates of >65% with resection, in patients without nodal involvement. Approximately 4% of lung cancers present as a solitary pulmonary nodule are SCLC (5) and therefore could be candidates for surgical resection. However the

benefit of adjuvant chemotherapy in this setting is unclear. Also, given the rarity of this presentation, it is unlikely that a randomized clinical trial will ever be performed to answer this question. In this context the retrospective analysis conducted by Yang *et al.* using the National Cancer Database is very significant (6).

Yang *et al.* reviewed the records of 954 patients in the National Cancer Database, with resected pT1–2, pN0, M0 SCLC between 2003 and 2011 (6). Of the 954 patients, 566 (59%) received some adjuvant therapy. The majority of patients (n=544; 96%) received chemotherapy, either alone (n=354) or with radiation (n=190); ninety-nine patients received cranial radiation. Patients treated with adjuvant chemotherapy with or without radiation had a median OS of 66.0 months and a 5-year OS of 52.7%. The corresponding figures for patients who did not receive adjuvant therapy were 42.1 months and 40.4% respectively. On multivariate analysis, the receipt of adjuvant chemotherapy alone [hazard ratio (HR), 0.78; 95% CI, 0.63–0.95] or with brain radiation (HR, 0.52; 95% CI, 0.36–0.75) was associated with significantly improved survival as compared to

surgery alone. Increasing age, tumor size, and Charlson Deyo Comorbidity score of 2+ were associated with worse survival, while the performance of a lobectomy was associated with improved survival.

The nature of the database leads to significant limitations of this analysis. The exact nature of the chemotherapy and radiation performed cannot be ascertained. The authors assumed that additional therapy was given as adjuvant therapy and not for early relapses and defined adjuvant as chemotherapy and radiation therapy (whether to lung or brain) given within 5 and 8 months of surgery, respectively.

Although the NCCN guidelines recommend the use of adjuvant chemotherapy following resection, this based on extrapolation from the understanding of the biology of SCLC and limited data (7). The limitations of this retrospective analysis notwithstanding, these results are significant and should establish adjuvant chemotherapy as the standard of care in patients with resected, node negative SCLC.

Another interesting finding in this analysis is the 48% decreased risk of mortality with adjuvant chemotherapy and brain radiation. The brain is a common site of metastasis in SCLC and approximately 45% patients who obtain a complete response with initial therapy will present with brain metastases as the only site of relapse (8). Prophylactic cranial irradiation (PCI) is recommended for patients with LS-SCLC and a good performance status following completion of definitive chemoradiation (8,9). Given the biology of SCLC, it stands to reason that patients with extremely early stage SCLC, as in the Yang study would benefit too. Again, it is unlikely that a randomized trial evaluating the role of PCI in this population will be performed. Hence these results should establish PCI as the standard of care following resection and adjuvant chemotherapy for SCLC.

This study however does not clarify the role of chest radiation following surgery. There was no benefit to thoracic radiation, either with or without adjuvant chemotherapy. It is possible that the relatively small numbers precluded the identification of a significant clinical benefit, but there was a significant benefit with PCI in similar numbers of patients. Also, it is not clear due to the nature of the database whether thoracic radiation was given truly adjuvant or as a salvage option. In non-SCLC, the detrimental effect of post-operative radiation in N0 or N1 disease is well-known (10) and a similar phenomenon may be at play in SCLC as well.

The disappointing feature of this analysis is that despite

aggressive treatment in an extremely good-risk patient population, the 5-year OS was only 53%. It is unlikely that we will make much meaningful progress in SCLC with the existing approaches. Immunotherapy approaches seem promising and these and other novel approaches must be evaluated rapidly in order to improve outcomes in this disease.

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Footnote

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References

1. Lewis DR, Check DP, Caporaso NE, et al. US lung cancer trends by histologic type. *Cancer* 2014;120:2883-92.
2. Shepherd FA, Crowley J, Van Houtte P, et al. The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. *J Thorac Oncol* 2007;2:1067-77.
3. Stinchcombe TE, Gore EM. Limited-stage small cell lung cancer: current chemoradiotherapy treatment paradigms. *Oncologist* 2010;15:187-95.
4. Almqvist D, Mosalpuria K, Ganti AK. Multimodality Therapy for Limited-Stage Small-Cell Lung Cancer. *J Oncol Pract* 2016;12:111-7.
5. Kreisman H, Wolkove N, Quoix E. Small cell lung cancer presenting as a solitary pulmonary nodule. *Chest* 1992;101:225-31.
6. 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.
7. Kalemkerian GP, Akerley W, Bogner P, et al. Small cell lung cancer. *J Natl Compr Canc Netw* 2013;11:78-98.
 8. Arriagada R, Le Chevalier T, Borie F, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J Natl Cancer Inst* 1995;87:183-90.
 9. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999;341:476-84.
 10. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. *Lancet* 1998;352:257-63.

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