

# Surgery for limited-stage small cell lung cancer: ready for prime-time?

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Small cell lung cancer (SCLC) represents approximately 13% of all newly diagnosed lung cancers in the United States (1). Around 40% of the patients present with limited-stage (LS) disease, and 60% with extensive-stage (ES) (1). LS mainly includes AJCC stages I–III patients, while ES includes stage IV patients (2). In the LS setting, cisplatin and etoposide (EP) concurrently with chest radiation is the current standard of care (3,4). However, patients with T1-T2, N0, M0 (stage I) with no pathologic mediastinal involvement can be considered for lobectomy and mediastinal lymph node dissection. In case postoperative pathology demonstrates metastases to hilar/mediastinal nodes, then adjuvant chemoradiation should be administered. If no evidence of nodal involvement, then adjuvant chemotherapy alone is recommended (5).

Wakeam and colleagues recently published an analysis, using the National Cancer Data Base (NCDB), which compared the survival outcomes among patients that underwent surgery to the ones that received chemoradiation in early-stage and locally advanced SCLC. The authors created a stage-specific propensity-matched analysis to further elucidate the survival difference between patients treated surgically and non-surgically in each stage group. In summary, a total of 2,089 patients with clinical stage I–IIIA SCLC underwent surgical resection and were matched 1:1 to those treated with chemoradiation. According to the study, surgery was associated with improved survival in all groups. For patients with stage I there was a significant survival difference [median OS 38.6 *vs.* 22.9 months, hazard ratio (HR) 0.62, 95%

CI: 0.57–0.69,  $P < 0.0001$ ], however it was not statistically significant for stage II (median OS 23.4 *vs.* 20.7 months, HR 0.84, 95% CI: 0.70–1.01,  $P = 0.06$ ). There was a significant survival benefit for patients with stage IIIA, but to a lesser degree (median OS 21.7 *vs.* 16.0 months, HR 0.71, 95% CI: 0.60–0.83,  $P < 0.0001$ ). Regarding the T and N staging, a longer OS was observed in resected patients with T3/T4 N0 (median OS 33.0 *vs.* 16.8 months,  $P = 0.008$ ), and in those with positive nodes (N1+ 24.4 *vs.* 18.3 months,  $P = 0.03$ ; N2+ 20.1 *vs.* 14.6 months,  $P = 0.007$ ). In patients with clinical stage I/II, a highly selected subgroup analysis matched 507 patients to chemoradiation, and 507 to lobectomy plus adjuvant chemoradiation. Trimodality treatment resulted in significantly longer survival when compared to chemoradiotherapy (median OS 28.7 months 95% CI: 24.6–32.7 *vs.* 48.6 months 95% CI: 40.7–59.1,  $P < 0.0001$ ). The authors concluded that surgical resection is associated with improved OS in early-stage and node negative SCLC.

Surgery was the mainstay treatment for SCLC until late 1960's. The treatment was shifted to concurrent chemoradiation after the United Kingdom Medical Research Council reported the results of a randomized study that compared pneumonectomy plus lymph node dissection to thoracic radiation in LS disease. Only 50% of the patients assigned to pneumonectomy underwent a complete resection, and 85% of the patients completed radiation. The 5-year survival was 1% and 4% with surgery and radiation, respectively (6). In the other prospective randomized trial, more than 300 patients received

cyclophosphamide, doxorubicin and vincristine (CAV), followed by resection plus thoracic radiation or thoracic radiation alone. No survival advantage was observed with the addition of surgery to induction chemotherapy and adjuvant radiation (7). Thus, given that only 5% of the patients with SCLC present with stage I disease, the vast majority of the data showing the benefit of surgery in early-stage are from small phase II and retrospective studies (8-12). Based on this data, after mediastinal staging, lobectomy plus lymph node dissection is a reasonable treatment option for good surgical candidates with T1-T2, N0, M0 SCLC. The study presented by Wakeam *et al.* supports the benefit of surgery for early stage disease, however it raises questions regarding the role of surgery in more advanced disease.

The evaluation of mediastinal lymph nodes is an essential component of the staging evaluation of patients with SCLC. It has been well established that pathological staging does not match with clinical staging. The IASLC staging project involved 349 patients with resected SCLC, making it the most comprehensive surgical series reported to date in the literature. A total of 144 patients with cN0 were analyzed and 14% was upstaged to pN2 or above after resection. On the other hand, clinical N2 was down-staged to pN1 or less in 32% of cN2 cases after resection. In the IASLC staging project, the correlation between clinical and pathological TNM was only 58% (2). So, is this basket filled with only apples? Given the uncertainty of how well these patients were stage, this "basket" might have some oranges mixed with apples and conclusions are difficult to make in this context.

Putting the IASLC data in perspective, more than 30% of patients with clinical N2 disease do not have truly stage IIIA. Actually, they have stage I or II disease. The study presented by Wakeam *et al.* had 401 patients with stage IIIA, which is a very high number of patients undergoing surgery for this stage. It turns out that approximately 120 patients underwent surgery for clinical stage III, but ended up with pathological stages I and II. Given this degree of mismatch, it is difficult to conclude that patients with stage IIIA derive benefit from surgery.

In patients with stages I and II, a subgroup analysis found that trimodality therapy was associated with significant survival benefit when compared to chemoradiation alone in those patients with lymph node involvement. This was a highly selected healthy population of patients with stage I and II SCLC, nevertheless the survival difference was very significant. The survival of 48.6 months in the trimodality arm versus 28.7 in the chemoradiation arm is

very appealing. However, these results must be taken in the context of the results of previous randomized trials. A prospective randomized trial with 328 patients performed by the Lung Cancer Study Group in 1994 demonstrated that induction chemotherapy, followed by surgery, and then radiation did not improve survival compared with chemotherapy followed by radiation (7). The Lung Cancer Study Group trial analyzed trimodality therapy in a sequential approach. Perhaps, surgery followed by concurrent chemoradiation would have a different impact on survival? Possibly, but only a randomized trial would be able to answer this question.

The role of surgery in patients with T1-T2, N0, M0 (stage I) with no pathologic mediastinal disease is based on small, retrospective, and single institution studies. Only 2 prospective randomized trials have evaluated surgery in SCLC, and both of them failed to demonstrate a survival benefit. Surgery should not be offered to patients with any degree of lymph node involvement (N1/N2/N3), and an aggressive mediastinal staging is extremely important to investigate for occult nodal disease. While it is very tempting to use the results of Wakeam *et al.* to change practice, it must be remembered that this is a retrospective analysis and the group of patients who received surgery is a highly selected group of patients. The reasons as to why they were operated upon are unclear and may have a significant impact on the results. Retrospective database analyses are mainly hypothesis generating and should be treated as such. These and more recent results have raised important questions regarding the role of surgery in limited stage SCLC. While not ready for prime time yet, there is enough evidence to support the conduct of a randomized, prospective clinical trial to answer this question. While such a trial could take many years to complete, better later than never!

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### Footnote

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

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