

## Upstaging, not just a non-small matter

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We thank Saji *et al.* and appreciate their thoughtful commentary on our work including its place in the context of the existing small cell lung cancer (SCLC) literature (1). Historically, the management of SCLC has relied heavily upon chemotherapy or chemoradiotherapy without surgery, including patients with early-stage disease (2-5). These recommendations are based, in large part, on randomized clinical trials that demonstrated no improvement in survival for patients who underwent surgery compared with those who received nonoperative treatments (6,7). However, a limitation of these influential trials may have been that they were conducted in an era prior to important advances in the preoperative staging, surgical resection, and adjuvant treatments of SCLC utilized commonly in the current era (8,9).

Many of the previously discussed studies describe data ranging from 1988–2005, while the current study describes a more modern era of treatment from 2004–2013. Our data demonstrates an important update to the literature of the surgical treatment of SCLC, as these data represent 5-year overall survival of patients treated in the modern era of adjuvant treatments, including contemporary radiation therapy techniques (10).

The average 5-year overall survival reported in the current study aligns with prior national database analyses evaluating surgically treated SCLC patients, which are described in Table 1 of the commentary by Saji *et al.* (10-14). Similarly, the occurrence of pathologic upstaging at the time of surgical resection described in the current study falls in line with the data from these prior studies, ranging from 19% to 25% (10,11,14).

The most exciting finding from our study was the 35% absolute difference in 5-year overall survival in

pathologically upstaged patients treated with chemotherapy and radiation therapy compared to chemotherapy alone (10). Additionally, the multivariable analysis identified the addition of adjuvant radiation therapy as significantly lowering the likelihood of overall mortality in patients with pN1 and pN2 disease. Unfortunately, there is limited data to benchmark our findings.

Currently, the National Comprehensive Cancer Network and the American College of Chest Physicians guidelines recommend curative-intent surgery as the initial treatment only for patients with early stage, node negative disease (2,5). As the current commentary notes, there is a growing body of evidence demonstrating favorable outcomes for patients who undergo surgical resection as their index treatment (15,16). This progress has led to a reevaluation of the role of surgery in the treatment of SCLC and an accompanying reevaluation of adjuvant therapies, as surgical resection is considered for an increasing number of SCLC patients. Furthermore, as surgical resections for SCLC increase, the potential for pathologic upstaging (pN+) may also increase accordingly. This clinical dilemma has been demonstrated to be a persistent occurrence despite advances in preoperative staging methods (17-19).

The indications for adjuvant radiation therapy following surgery in the setting of SCLC are not well defined. Current consensus guidelines concerning adjuvant therapy of patients pathologically upstaged at the time of surgical resection either do not address the use of chemotherapy or radiation therapy specifically or simply recommend the use of both (2-5). The discrepancy among recommendations stems from the lack of available data on this clinical quandary. As Saji *et al.* aptly note, the current guidelines are formed partially from the demonstrated efficacy of

concomitant chemoradiation therapy for limited-stage disease (1,20).

Two of the four national database analyses highlighted by Saji *et al.* (Table 1) discuss the occurrence of pathologic upstaging, and only one was able to assess the impact of adjuvant treatment in upstaged patients (11,14). Of these studies, the study by Takei *et al.* most closely resembled the current study in its ability to determine the impact of adjuvant treatment on pathologic upstaging in SCLC, by evaluating the impact of adjuvant chemotherapy (14). However, the specific treatment of those pathologically upstaged was not reported and no patients were treated with adjuvant radiation therapy (14). Other comparable studies include those analyzing the National Cancer Database (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) database, which report conflicting results with regard to the survival advantage of adjuvant radiation therapy. These studies report a range of outcomes, from a survival benefit for patients with pN2 disease, to no difference in survival for patients with nodal disease (21-23).

Similar to SCLC, the role of adjuvant radiation therapy in the non-small cell lung cancer (NSCLC) literature has long been debated due to the conflicting results of retrospective studies and nonrandomized trials on the survival benefit of adjuvant radiation therapy after surgical resection (24-26). Recently, there has been a reevaluation of its role in patients both with and without nodal disease, as much of the data suggesting no survival benefit to adjuvant radiation therapy was based on historical studies (27). Indeed, a meta-analysis of patients with stage III NSCLC demonstrated that modern adjuvant radiation therapy may improve local control and overall survival (28). A similar reevaluation also has occurred in SCLC due to concerns that knowledge on this topic emerged from a prior era of radiation therapy that utilized older technology. These outdated approaches frequently utilized two-dimensional radiotherapy, cobalt-based radiotherapy, and unacceptably large doses per fraction (29). Improvements in radiation therapy planning and delivery decrease treatment morbidity by better targeting treatments to spare surrounding tissue while delivering adequate doses to the target margins and nodal basins (30).

Our data highlights the changing landscape of SCLC and the challenges that remain. Upstaging after surgical resection of SCLC remains a very real occurrence and the presence of nodal disease after surgery is associated with an inferior 5-year overall survival. These data add to the

growing base of evidence that support the role of surgery as part of a multimodal treatment algorithm for patients with early-stage SCLC. Furthermore, the addition of adjuvant radiation therapy may significantly improve 5-year overall survival when given in addition to adjuvant chemotherapy in patients with nodal disease identified at surgery. These data suggest that SCLC patients may benefit to pursuing aggressive local control with both surgical resection and adjuvant radiation therapy. Further studies should continue to evaluate the role of surgery and adjuvant therapies in the treatment of SCLC, including randomized trials to evaluate the efficacy of adjuvant radiation therapy in the setting of nodal disease after surgery.

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### Footnote

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

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