Positive margins after lung cancer surgery: is postoperative radiotherapy worth the burn?

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Surgical resection margins are a key quality metric for in the surgical management of non-small cell lung cancer (NSCLC), and margin status influences local recurrence and long-term survival (1). While the importance of negative surgical margins is accepted, the optimal adjuvant treatment strategies, and in particular the role of post-operative radiotherapy (PORT), are less clear. Current evidence for the role of PORT in NSCLC comes from early randomized trials (2,3) and meta-analyses (4,5) that suggest PORT may confer better locoregional recurrence rates and survival in N2 node-positive patients but potentially worse survival in early stage disease that has been resected with negative margins. Current National Comprehensive Cancer Network (NCCN) and American Society of Radiation Oncology (ASTRO) guidelines suggest that early stage margin-positive NSCLC (IA–IIB) be re-resected or treated with PORT ± adjuvant chemotherapy, and incompletely resected IIIA/B disease be treated with adjuvant chemoradiation (6,7). Here we review an analysis published in *The Journal of Thoracic and Cardiovascular Surgery* in August 2017 by Smeltzer *et al.* (8) that attempts to address this controversial topic.

The authors present a retrospective analysis of the National Cancer Database (NCDB) looking at survival of patients with resected NSCLC (8). They compare the effectiveness of four adjuvant strategies following resection with macroscopically or microscopically positive margins: observation, chemotherapy alone, radiotherapy alone, or combined chemoradiation. The study population includes patients with pathological stages I–IIIA NSCLC from 2004–2011 stratified into one of four groups based on pathological stage: (I) stage IA (T1ab, N0); (II) stage IB (T2a, N0) and stage IIA (T2b, N0); (III) stage IIA (T1ab–T2a, N1) and stage IIB (T3, N0; T2b, N1); and (IV) stage IIIA (T1–3, N2; T3, N1). The authors exclude patients undergoing neoadjuvant therapy, any patient who died within 60 days of surgery, and patients undergoing re-resection of residual disease. The primary outcome was 5-year overall survival (OS). Kaplan-Meier survival curves and multivariable Cox models were used to compare survival across groups.

The authors identify 3,461 patients who underwent R1/R2 resections. Of these, 60 stage IA and 119 stage IB–IIA (N0) patients who received adjuvant radiation were found to have worse 5-year OS compared to patients of the same stage who did not receive radiation (25–26% *vs.* 47–58%, $P<0.05$) (8). In these early stage node-negative patients, chemotherapy alone was associated with longer survival but there was no association between survival and combined chemoradiation. In patients with more advanced disease (stage IIA with N1 node positivity or stage IIB and IIIA), both chemotherapy alone and chemoradiation were associated with longer survival, but no survival association was observed with radiation alone (8).

To validate their analytic approach, the authors compared survival of R0 patients stratified by the same stage groups and adjuvant treatment modalities as the R1/R2 patients. They found that adjuvant PORT alone was not associated with a significantly longer 5-year OS in any of the subgroups, but its combination with adjuvant chemotherapy was associated with improved survival in groups 3 and 4 [stage IIA (T1ab–T2a, N1) to stage IIIA (T1–3, N2; T3, N1)] (8). These results support the current NCCN recommendations for margin-negative resections. The R0 analysis suggests that the effectiveness estimates in the authors' main analysis should approximate reality (6).

While the article is thorough and rigorously executed, there are some limitations. Firstly, the definition of adjuvant therapy that the authors have chosen is broad. The authors considered radiotherapy administered within 6 months after surgery at any dose and fractionation scheme, and those patients receiving sub-therapeutic doses of radiation or an incomplete course of chemotherapy could potentially have been misclassified. The conclusions reached by the authors regarding adjuvant radiotherapy may have been strengthened by a sensitivity analysis since PORT was the primary exposure studied. The authors argue that a broad definition creates a more "real world" estimate, and likely biases the conclusions towards conservative estimates of the effects of adjuvant radiotherapy (8). This may partially account for the lack of association between PORT and survival in some of the analyses. Secondly, patients who died within 60 days of surgery were excluded, which could also bias the results. The median time from surgery to adjuvant therapy in all four groups was less than 60 days; therefore, by definition, at least half of the 6,166 patients who died within 60 days had received some form of postoperative therapy (8). If one of the adjuvant therapies increases the risk of death within 60 days following surgery, these patients would be excluded from the analysis. This could falsely result in more favourable survival outcomes for that strategy. Reporting the 60-day mortality rates across the four adjuvant therapy groups would aid in assessing the risk of bias.

Other groups have also used the NCDB to analyze the possible utility of PORT for both margin-negative and margin-positive subgroups. Gulack *et al.* found no significant OS differences between margin-positive stage I and II NSCLC patients receiving PORT and non-irradiated patients (HR_{PORT} 1.10, 95% CI, 0.90–1.35, P=0.353) (9). PORT additionally was not associated with improved survival in sensitivity analyses of patients with R1 disease or those with pathological stage N0. The authors accordingly argue against the use of PORT in early-stage NSCLC in keeping with the results presented by Smeltzer *et al.* Another investigation by Wang *et al.* used the NCDB but derived different conclusions (10). They included patients with stage II/III margin-positive NSCLC after either lobectomy or pneumonectomy. Importantly, this study restricted PORT dosage to 50–74 Gy and excluded those who died within 4 months of diagnosis (10). Median survival times were longer for patients treated with PORT (33.5 *vs.* 23.7 months, P<0.001), and these associations remained significant following multivariable Cox model adjustments, nodal stage stratification, and propensity score matching (10). Unlike Smeltzer *et al.*, Wang *et al.* excluded stage I patients, which may account for some of the differing conclusions reached by these two groups. While inclusion of sub-optimal radiation doses may give more "real world" approximation of practice, the decision to include these patients may also blur the potential impact of therapeutic radiation doses on survival.

In summary, Smeltzer *et al.* present a significant study providing evidence for the management of patients with incompletely resected NSCLC, an area in which guidelines are largely based on expert opinion. Their analysis may guide decision-making while we await definitive randomized evidence. In the context of several studies with conflicting results, the clinical implications of Smeltzer and colleagues' work are not fully clear. These varying results may reflect the clinical heterogeneity of the margin-positive population presenting for adjuvant radiation (11). Anatomic considerations, patient factors, and the overall burden of disease heavily influence adjuvant treatment decisions, especially with respect to further local therapy. Future studies will need to focus on these varying subgroups in order to clarify whether radiotherapy is indeed worth the burn for margin-positive patients after NSCLC resection.

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