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Commentary: Meta-analysis of postoperative radiotherapy in N2-positive lung cancer—Garbage in, garbage out?

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Differences abound regarding the management of surgically resectable stage IIIA non-small cell lung cancer (NSCLC), as this clinicopathologic designation comprises a complex, highly heterogeneous group of patients.¹ In Europe, primary operations for N2 disease may be more prevalent, whereas in North America there is a widely subscribed tendency to undergo lung surgery after induction chemoradiotherapy.^{2,3} In stage IIIA N2-positive patients with adjuvant chemotherapy after curative resection, the survival benefit of postoperative radiotherapy (PORT) has been a topic of ongoing debate.

In this issue of the *Journal*, Harling and colleagues⁴ provide an updated meta-analysis of NSCLC patients who have undergone more contemporary radiation therapy (RT) in the era of routine adjuvant chemotherapy. Ten studies reporting on treated patients from 1994 to 2011 were analyzed by random-effects modeling, and subgroup analysis was performed using meta-regression. The pooled dataset consisted of 18,077 patients, with 30.2% receiving PORT and 69.8% not receiving PORT. Three studies were prospective, and 3 were evaluations of the National Cancer Database at various historical time intervals. PORT was randomized in only in 2 studies (n = 172 patients) that terminated early because of

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CENTRAL MESSAGE

Postoperative radiotherapy (PORT) is shown to improve survival in this updated meta-analysis; however, multiple data limitations soften the enthusiasm for any true PORT benefit.

slow recruitment. Surgical resection details were available for only 27.6% of the patients, with 79.7% undergoing lobectomy, 11.3% undergoing sublobar resection, and 8.6% undergoing pneumonectomy. There were significantly more pneumonectomy patients in the no-PORT group ($P = .001$) and more T3 patients in the PORT group ($P = .04$). At 1, 3, and 5 years, the PORT group had significantly improved durations of overall survival (OS) and disease-free survival (DFS) compared with the no-PORT group. Meta-regression of multiple characteristics did not identify any independently significant associations with OS or DFS.

We congratulate the authors for their expert biostatistical assessment, but the many limitations inherent in the available datasets for this analysis should give everyone pause as to their overall conclusions. In addition to their acknowledgments, several broad limitations should be emphasized, including the lack of high-granularity data at the patient level stemming from retrospective collective analyses, the heterogeneity of both patient populations and therapeutic schemes stemming from changing clinical definitions over long time spans that persisted despite statistical adjustments, and, finally, the multiple unknown selection biases and unidentified sources of confounding from nonrandomized studies. It is prudent to keep in mind that nonrandomized studies tend to show larger treatment effects that in fact might not be true, and so pooling of these kinds of reports may not routinely arrive at high-confidence conclusions. Regarding specific caveats with this meta-analysis, most

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concerning is the lack of details on radiotherapy dose and planning techniques across the studies under review.

These limitations temper the strength of the authors' pro-PORT conclusions and recommendations. Early results from the international randomized Lung_ART trial ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier NCT00410683), directly studying modern mediastinal PORT, have not been formally published but were recently presented in an abstract.⁵ This prospective trial randomized 501 NSCLC patients (accrued from 2007 to 2018) after lung resection with pathologic N2 disease to PORT (54 Gy; 252 patients) or no PORT (249 patients), with most receiving chemotherapy (adjuvant, 77%; neoadjuvant, 18%). At a median follow-up of 4.8 years, preliminary findings showed no significant difference in 3-year DFS or OS between the study groups, with higher cardiopulmonary toxicity in the PORT group. Interestingly, the 3-year DFS and OS were higher than expected in both study arms, while mediastinal relapse was reduced by 50% in the PORT arm. The final results of this latest trial for PORT may provide succinct clinical guidance for this therapeutically challenging subgroup of NSCLC patients. It will be interesting to see whether future meta-analyses

arrive at a different conclusion regarding the impact of PORT than that reached by Harling and colleagues.

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