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Perspectives on Postmastectomy Radiation Therapy for Persistent Nodal Disease After Neoadjuvant Chemotherapy: Is Hindsight 20/20?

Grace L. Smith, MD, PhD, MPH*,†

*Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

†Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, Texas

Postmastectomy radiation therapy (PMRT) generally improves locoregional control and overall survival in patients with pathologic lymph node-positive breast cancer, as evidenced by meta-analyses of randomized trials (1). Nevertheless, controversy persists regarding whether PMRT is indicated for all such patients, especially those with clinical T1-T3N1 who receive neoadjuvant chemotherapy (NAC) with a complete pathologic response in the involved axillary lymph nodes (ypN0). For such patients, the current standard recommendation is to offer entry into clinical trials comparing regional nodal irradiation (RNI) versus no RNI (2), such as the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-51/Radiation Therapy Oncology Group 1304 trial.

For patients with persistent—but low burden—nodal disease, clinical decision-making for RNI remains ever-challenging, especially with the increasing use of NAC in breast cancer patients (3). The current default standard recommendation is still for PMRT for patients with any persistent nodal disease after NAC (2). However, in the report that accompanies this editorial, Ohri et al (4) reported only 57% use of PMRT in patients with ypN1 disease and, surprisingly, only 67% use in patients with ypN2 and 65% in patients with ypN3 disease. These data were derived from the National Cancer Database (NCDB), a comprehensive reporting source of oncology practice patterns from accredited cancer treatment facilities in the United States. Such low usage rates suggest that in actual practice, considerable enduring debate continues regarding the utility of PMRT after NAC, even in patients with a residual nodal burden. Without an ongoing national prospective randomized trial focused on defining the benefit of PMRT for patients with residual nodal disease (ypN+), akin to NSABP B-51 for ypN0 patients, we must rely on retrospective and secondary analyses such as that by Ohri et al (4) to offer clinical perspectives on the ongoing debate.

This retrospective study analyzed the survival outcomes associated with PMRT in 11,628 breast cancer patients with persistent nodal disease after NAC (4). In multivariate analyses of

patients with ypN1-N3 disease, no overall survival benefit was associated with PMRT. In subsidiary analyses, a small, but significant, relative survival benefit was detected only for patients with ypN3 disease (hazard ratio [HR] 0.836; 95% confidence interval [CI] 0.731–0.57; $P=.009$ for all-cause mortality). The adjusted HRs for patients with ypN1 and ypN2 disease, in contrast, remained essentially null. Notably, these results were obtained from a large, nationally comprehensive, and relatively contemporary patient sample.

Does their retrospective study, with its strengths, provide sufficient evidence in hindsight that PMRT offers no survival benefit to breast cancer patients with ypN1-N2 disease? Unfortunately not. A previously reported study by Rusthoven et al (5) similarly analyzed the data from 7243 postmastectomy patients with persistent nodal disease after NAC, also derived from the NCDB database. In contrast to the result reported by Ohri et al (4), Rusthoven et al (5) demonstrated not only an overall survival benefit associated with PMRT for all patients with ypN+ disease (HR 0.772; 95% CI 0.689–0.866; $P<.001$ for all-cause mortality), but also benefits across the subsets of patients with ypN1 (HR 0.835; 95% CI 0.713–0.978; $P=.0026$) and ypN2-N3 (HR 0.678; 95% CI 0.574–0.800; $P<.001$) disease. These findings contradicting those reported by Ohri et al (4) occurred even with the substantial overlap between these 2 studies in the data from several thousands of actual patients included in the analyses.

With apparently opposite verdicts, a comparison of these 2 studies must be undertaken to identify the reasons for the differences. First, the 2 studies differed in their patient selection criteria. The analysis by Rusthoven et al (5) included a presumably more homogeneous sample, selecting only patients reported to the NCDB with clinical stage T1-T3N1 disease (favoring internal validity). The clinical homogeneity of this study group is underscored by the substantially greater rates of PMRT reported by Rusthoven et al (5), 71% for ypN1, 82% for ypN2, and 81% for ypN3 patients. In contrast, the study by Ohri et al (4) included patients with any clinical stage, ostensibly to be more clinically pragmatic and inclusive (favoring external validity). Nonetheless, expanding the inclusion criteria would have presumably allowed for both lower risk patients—with clinical N0 disease—and higher risk patients—with clinical T4 and N2-N3 disease. This heterogeneity could have biased the results toward the null, in particular, for the outcome of overall survival, which is sensitive to both locoregional and distant relapse risks, which are fundamentally different for lower and higher risk patients with regional disease (1). The survival outcomes were not adjusted for the upfront clinical stage; therefore, fundamental differences in the baseline clinical risks might not have been fully reflected in the model (4). The studies' contrasting approaches elucidate an important lesson for future study design and results interpretation: extraordinary care must be taken in patient selection for retrospective analyses given the effect of patient selection on both the clinical and the statistical significance of the findings.

Second, the 2 studies differed in their modeling approaches. Ohri et al (4) included substantially more covariates (potential confounders), including pathologic and clinical and treatment variables, and imputed missing values for these variables. In contrast, Rusthoven et al (5) used “ad hoc” approaches to account for missing values, which could have led to unintended biases (6). Although a comprehensive review of the strengths and weaknesses of statistical modeling approaches is beyond the scope of this report, a fundamental principle to

acknowledge is that when large population data such as those in the NCDB are assembled from multiple sources, inevitably data (including death data) will be missing (7). What at first appears to be a very reasonable rate of 6% for missing covariate data for each individual variable, including treatment (PMRT) and outcome (survival) variables, ultimately easily translates into “missingness” affecting >40% of the analytic sample—a potentially meaningful obstacle to obtaining the least-biased model.

The field of radiation oncology is moving toward an increasing reliance on “big data” sources to answer clinical questions and guide the practice of multimodality care. These sources include not only historically popular sources such as the NCDB and Surveillance Epidemiology, and End Results program, but also comprehensive, rapid-learning data collection systems, such as CancerLinQ. This reliance underscores the importance of quality ascertainment of oncology data, including radiation treatment details and cancer outcomes. The accuracy of such data has the potential to affect substantively the interpretation of research findings, as exemplified by the differences in the designation of “PMRT” for Ohri et al (radiation with a documented dose of 45 to 65 Gy; a more specific definition) versus Rusthoven et al (radiation to the chest wall with or without the lymph nodes; a more sensitive definition). Without a dedicated analysis directly comparing the definitions, it is impossible to parse out the potential biases lent by one definition versus another. However, one can hypothesize several biased scenarios. If the reporting quality on radiation dose details was associated with quality ascertainment of deaths, this could artificially weaken the association between radiation therapy and survival. Alternatively, if a too-sensitive definition of radiation included palliative, undelivered, or an incomplete radiation course, this could artificially strengthen the association. At a minimum, the inconsistency between the 2 studies highlights the lack of scientific consensus on the most basic of definitions, the seemingly simple dichotomous classification of radiation treatment: “yes versus no.” Furthermore, such inconsistency demonstrates the genuine challenge in practice of translating assorted clinical details about radiation treatment into working research data to address real-world knowledge gaps.

In conclusion, the findings reported by Ohri et al (4) fuel ongoing questions about the optimal role of PMRT for patients with persistent nodal disease after NAC. Their divergence from an ostensibly similar study highlights the understandable skepticism that exists about whether retrospective studies can offer meaningful clinical insights. This divergence of findings, however, could also stimulate a complementary response, that of a heightened awareness for foresight in the field of radiation oncology to design learning systems that achieve quality data collection, reporting, and analysis. Insightful system design will foundationally serve the field of oncology by supporting ongoing research designs that can ultimately provide satisfying clinical conclusions about the role and effectiveness of radiation treatment.

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