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Editorial

Benefit vs Harm of Internal Mammary Node Irradiation for Node-Positive Breast Cancer

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There has been ongoing debate for decades regarding adjuvant regional nodal irradiation for axillary node-positive breast cancer patients, in particular, about whether the relative benefit of targeting the internal mammary nodes (IMN) as part of this treatment offsets its potential harms. The publication from Poortman et al. (1) in this issue of the Journal that reports side effects 15 year after randomization to regional nodal irradiation with IMN vs not on the large European Organization for Research and Treatment of Cancer, EORTC 22922/10925 trial provides valuable long-term data to address this. At 15 years of follow-up, those randomly assigned to IMN irradiation had a 2.7% and 2.8% higher cumulative incidence of any cardiac disease and clinical evidence of lung fibrosis, respectively. Most morbidity was grade 1, and there was no statistically significant difference in the incidence of grade 2 or higher cardiac or pulmonary toxicity. There was no difference in cardiac toxicity incidence between right- vs left-sided breast cancer or in the incidence of second malignancies, contralateral breast cancer, or cardiovascular deaths with IMN radiation.

The debate about IMN radiation dates back 30 years when publications like Auguier et al. (2) analyzed the Oslo II and Stockholm postmastectomy randomized radiation trials conducted in the presystemic therapy era, which identified an interaction between regional nodal irradiation benefit and axillary lymph node status. Specifically, patients with positive axillary nodes who received regional nodal irradiation inclusive of the axillary, supraclavicular, and IMN had improved distant metastases-free survival. Any emerging benefit of regional nodal irradiation that was reported was soon overshadowed by the observation of excess cardiac-related death occurring after 10 years of follow-up from radiotherapy in a meta-analysis of 10 randomized clinical trials that were conducted prior to 1975 (3). The highest cardiac-related death rates occurred in 3 of the oldest trials and were associated with methods aimed at delivering a high dose to the IMN. Since then, multiple randomized trials conducted in a more modern era in conjunction with systemic therapy have consistently demonstrated that regional nodal irradiation, including the IMN postmastectomy or lumpectomy, results in reduced local regional recurrences and systemic events, as evidenced by either statistically significant reductions in distant disease rates, breast cancer mortality, or improvements in disease-free survival (4-7). Even more compelling, the outcome of 2 clinical trials specifically evaluating inclusion of the IMN in regional nodal irradiation demonstrated that it provided statistically significant incremental cancer control benefit (8-10). As a result, 2016 updated guidelines addressing postmastectomy radiotherapy recommended that internal mammary nodes "should generally be treated" as part of regional nodal irradiation (11). Yet, it stressed that balance is needed against the known pulmonary and cardiac morbidities that are of concern even with improved radiotherapy techniques.

Techniques for delivery of regional nodal irradiation have improved over time, leading to less injury to adjacent normal tissue. Simply analyzing by treatment era, reduction in excess cardiac mortality rates are seen from radiation of the left breast compared with the right (12). In this analysis from Surveillance, Epidemiology and End Results (SEER) data regarding radiation between 1973 and 1988, the excess cardiac mortality rate was no longer present for women diagnosed in 1988. Importantly, awareness of the risk for excess cardiac toxicity that potentially obliterates the treatment benefit has driven researchers to identify a radiation dose threshold for cardiac toxicity and to incorporate advanced technology to achieve more cardiac sparing. Over the past decade, this includes heart atlases to guide dose constraints in treatment planning (13), implementation of breath hold to move the heart out of the radiation treatment field (14), and delivery methods like intensity-modulated radiation therapy and protons for those with unfavorable anatomy for cardiac sparing (15,16). The net effect is seen in an overview of 99 publications of breast cancer radiation, which reported that since 2014, the mean dose to the heart decreased by nearly 50% (17). The effectiveness of these measures to ameliorate cardiac toxicity will unfortunately be unknown for some time because of the long latency of onset post-breast cancer radiation. In the interim, retrospective evaluation of existing databases in combination with modeling of mean heart dose (MHD) using current treatment planning methods has provided some guidance. A population-based study of 2168 breast

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cancer patients treated from 1958 to 2001 in Denmark estimated that MHD was 4.9 Gy and observed a linear dose-effect correlation between rates of major coronary events and modeled heart doses (18). The risk of major coronary event increased by 7.4% per Gy delivered to the heart on average and for node positive cases 11.8% per Gy. A more recent analysis estimated that MHD was 4.4 Gy based on 214 publications from 2010 to 2014 (19). The excess rate ratios for cardiac and lung mortality were calculated from a meta-analysis of 40 000 women in 75 breast cancer radiation randomized trials from 1951 to 2000, and median follow-up was 10 years. An estimated excess risk ratio for cardiac mortality of 0.041 per Gy was found, corresponding to an excess cardiac death rate of 0.3%-1.2% depending on smoking history. An excess lung cancer risk of 0.11 per Gy whole lung dose corresponded to a long-term lung cancer risk of 4% for smokers and 0.3% for nonsmokers.

Although there were more cardiac events at 15 years from IMN radiation on the EORTC 22922/10925 trial, the incidence appears less than estimated by the analyses above, and there were no excess secondary malignancies (1). This likely reflects that despite radiation methods on this trial being prior to recent cardiac-sparing approaches, it was sufficiently more modern than what was studied in prior analyses. Unfortunately, individual computed tomography scan–based radiation plans are not available on this trial so the correlation of cardiac toxicity with dose to the heart and heart substructures is not possible. Now, clinical trials evaluating breast cancer radiation routinely collect this technical information and will be able to provide this important dose response data. It is essential to recognize that estimates of cardiac events do not provide insight on the clinical morbidity of the event and its impact on the patient. The majority of cardiac toxicity was grade 1 with no statistically significant difference in the incidence of grade 2 or higher events. Improved monitoring, early detection, and treatment of radiation-induced cardiac disease may be a means of minimizing the clinical effect of the toxicity, and research is ongoing. These long-term side effects from IMN radiation move us one step closer to resolving the debate about the value of IMN radiation, and EORTC is commended for collecting this long-term toxicity data that informs clinical practice.

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