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Cardiac Morbidity and Radiation Therapy for Breast Cancer

By Jean Wright, MD, Rachel Blitzblau, MD, PhD, *Associate Senior Editors*

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The relationship between radiation treatment for breast cancer and subsequent risk of cardiac morbidity and mortality has been known for decades (1, 2), but risks in the modern era are less clear and seem to be significantly lower than in prior eras (3-5). There have been significant improvements in technology and awareness, allowing more nuanced dosimetric analysis and attention to cardiac exposure in patients treated with modern computed tomography (CT)—based planning, but long-term follow-up with more modern techniques is limited. Nonetheless, given the excellent long-term survival in breast cancer patients, the impact of cardiac risk on posttreatment survivorship has come to the fore. To date, there are no published randomized radiation studies with an endpoint of cardiac events, though there is a great deal of emerging data on potential surrogates for cardiac risk, such as strain and single photon emission computed tomography imaging (6-8). The RADCOMP Pragmatic Randomized Trial of Proton versus Photon Radiation for Stage II-III Breast Cancer is under way (clinicaltrials.gov/ct2/show/NCT02603341) and will report on the relationship between radiation dose to the heart and major cardiac events. In the interim as we await these data, a number of recent publications warrant the attention of the radiation oncologist to inform clinical decisions and radiation planning details.

Van den Bogaard et al. Validation and modification of a prediction model for acute cardiac events in patients with breast cancer treated with radiotherapy based on three-dimensional dose distributions to cardiac substructures. *J Clin Oncol* 2017. (9)

Summary: Van den Bogaard et al present a validation study of the landmark analysis of the relationship between mean cardiac radiation dose from breast cancer treatment and subsequent risk of acute coronary events (ACEs) published by Darby et al in 2013 (10). The study consists of a cohort of 910 women treated with adjuvant radiation for breast cancer using 3-dimensional (3D) conformal CT-based planning between 2005 and 2008. Using an autosegmentation algorithm based on the validated cardiac anatomy atlas by Feng et al (11), the heart and key substructures, including the left ventricle, were contoured, and individual dose-volume histograms generated. The cumulative incidence of ACEs was analyzed, accounting for age, cardiac risk factors, and cardiac dosimetric parameters. The mean heart dose (MHD) was 2.37 Gy (right 1.31 Gy, left 4.44 Gy), and the authors found a relationship similar to that reported by Darby et al, with a cumulative incidence of ACE at 9 years of 16.5% per Gy (median follow-up 7.6 years). A normal tissue complication probability model was generated and optimized. Both MHD and the volume of left ventricle receiving 5 Gy (LV-V5) were found to be correlated with the risk of ACE, with LV-V5 having the strongest correlation. In addition, both age and a weighted ACE risk score were significantly associated with ACE risk. The overall estimated cumulative incidence of ACE at 9 years was low at 3.5%, and the excess cumulative risk attributable to radiation therapy (RT) was 1.13%.

Comments: The 2013 publication of an analysis by Darby et al on the risk of ischemic heart disease after radiation therapy for breast cancer in the *New England Journal of Medicine* (10) drew widespread attention and public awareness to the dose-response relationship between radiation exposure and cardiac events. However, there were important limitations to that study, most importantly that the analysis was based on a single CT scan with "typical" cardiac anatomy. Radiation oncologists recognize the wide variability in cardiac anatomy from patient to patient and called into question the estimates of mean cardiac dose in a large cohort of patients based on a single representative scan. The analysis by van der Bogaard et al marks a

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significant advance in our understanding of these dose-volume relationships in providing a patient-specific dosimetric analysis. Many radiation oncologists have suspected that MHD may be a surrogate for dose to more specific cardiac substructures, such as the left anterior descending artery or the left ventricle, and the finding that the LV-V5 had a stronger correlation with ACE risk than MHD is compelling. The accompanying editorial in the *Journal of Clinical Oncology* by Abram Recht (12) highlights the significance of these findings in more detail and urges validation of the LV-V5 by other groups. To provide this validation, it would make sense for many of us to begin to evaluate the LV-V5 in routine clinical practice, even if a concrete dose constraint cannot be derived from the available data. It is also important to note that the overall risk of ACE was very low in this analysis, and specifically that the excess risk attributable to RT is small. Therefore the decision to compromise clinical coverage in favor of cardiac/left ventricle sparing in the setting of known risk reduction with the addition of radiation therapy in selected settings should be made with caution.

Taylor et al. Estimating the risks of breast cancer radiotherapy: Evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol* 2017. (13)

Summary: The Early Breast Cancer Trialists' Collaborative Group presents a new analysis of the relationship between radiation dose to the heart and lungs and the risk of late radiation sequelae, including both heart disease and second malignancy. The study has 3 elements: a systematic review of breast cancer radiation therapy dosimetry reports published in the period 2010 to 2015 to obtain "typical modern doses"; a meta-analysis including 40,781 patients from 75 randomized trials published between 2010 and 2015 (with studies accruing as early as the 1970s) to determine rate ratios (RRs) and excess rate ratios (ERRs) of late sequelae in these randomized trials; and an application of ERRs of late sequelae per Gy and modern RT doses to population mortality data. The systematic review of "modern" dosimetry reports demonstrated an average whole-heart dose of 4.4 Gy (right 3.7 Gy, left 5.2 Gy), whereas in the randomized trials the average reported whole-heart dose (where available) was 6.3 Gy. In the meta-analysis there was an increased RR of all-cause mortality among women without breast cancer recurrence (RR 1.15, 95% confidence interval [CI] 1.09-1.22), predominantly driven by cardiac disease (RR 1.3, 95% CI 1.15-146). The majority of ERR for cardiac mortality was from ischemic heart disease (ERR 1.31, 95% CI 1.13-1.53), and the ERR for cardiac mortality was 0.041 per Gy to the whole heart. Finally, the authors applied the "typical modern" whole-heart dose of approximately 4 Gy to the 0.041 ERR for cardiac mortality to estimate modern cardiac risk in smokers versus nonsmokers. They estimated that the absolute increase in cardiac mortality from radiation would be 0.3% for a nonsmoker and 1.2% for a smoker. Similar analyses were applied for second malignancies, including contralateral breast cancer.

Comments: This study tackles a great deal of data and requires several read-throughs to grasp, but it is worth the effort. There are significant limitations, notably the fact that the RR and ERR are based on treatments that were often delivered many decades ago, when RT and other aspects of breast cancer care were markedly different from the current era; risks in the present may be assumed to be significantly lower. The estimates are based on "modern" whole-heart doses of approximately 4 Gy, and many centers routinely deliver significantly lower doses than this (14, 15). Finally, because of limitations in data availability, the RRs are for mortality rather than cardiac events. However, as the authors point out, by estimating an ERR per gray, we may be able to apply these findings to our current patients, knowing the actual heart doses we deliver for each patient and taking into account their individual risk factors. The most unique aspect of the study is the analysis of the relationship of smoking history to RT risk. The study highlights the very small risks associated with RT in healthy nonsmoking women and urges individualization of therapy with assessment of patient-specific risk-benefit analysis in smokers. The focus of this Oncology Scan is on the cardiac findings, but the study also reports a wealth of data on second malignancy.

Wollschläger et al. 3D conformal radiotherapy is not associated with the long-term cardiac mortality in breast cancer patients: A retrospective cohort study in Germany (PASSOS-Heart Study). *Breast Cancer Res Treat* 2017. (16)

Summary: Wollschläger et al present a multicenter, retrospective, cohort study of long-term cardiac mortality data for 11,982 women treated for breast cancer in Germany between 1998 and 2008 (16). Individual patient data were abstracted from hospital records. Particular attention was given to pre-existing cardiac comorbidities. Death certificates were obtained and the cause of death coded according to the *International Classification of Diseases, 10th Revision*. Patients were treated with 3D conformal tangential fields, most commonly to 50 Gy in 25 fractions, often with 10-Gy tumor bed boost, and nodal field as needed. Time at risk was considered to be date of diagnosis to date of death or December 31, 2012. Multivariable Cox regression was used to assess effect of laterality for patients who did or did not receive RT, adjusted for potential confounders. A total of 2924 patients (24.4%) did not receive RT. In the women who received RT there was no difference in laterality or pre-existing cardiac factors. Detailed analysis of 769 individual patient RT plans showed an average MHD for left-sided RT of 4.6 Gy versus 1.7 Gy for right-sided RT. At the date of last follow-up, 36.4% of patients who did not

receive RT and 15.5% of patients who did receive RT had died, with cause of death ascertained for 95%. In the no-RT group heart disease accounted for 15.6% of all known deaths. In patients who did receive RT, heart disease represented 7.3% of deaths in right-sided patients and 7.7% in left-sided patients. The highest number of heart disease—related deaths in the RT group occurred 0 to 5 years after diagnosis, with very few seen at 10 to 15 years. No clear difference in mortality from heart disease for left- versus right-sided breast cancer patients was found. In multivariable analysis only pre-existing cardiac disease predicted for cardiac mortality.

Comments: As discussed above, cardiac risk from RT in the era of modern 3D conformal RT techniques is less clear. Though retrospective, this study has the distinct advantage of a large sample size and more detailed RT analysis than was possible in the Darby study. They also had a significant number of patients who did not receive RT and a nice balance between left- and right-sided cancers, without differences in pre-existing cardiac risk factors. The study is limited in its overall power by the low total number of cardiac events in the patients who received RT. However, this alone is important information, demonstrating the fortunately relative rarity of cardiac death in breast cancer patients treated with RT. The fact that they did not find a difference in cardiac mortality in left- versus right-sided patients who received RT with modern treatment planning and delivery highlights the importance and likely efficacy of utilizing these techniques to minimize dose to the heart. As previously mentioned, many centers are currently achieving lower MHDs than in this patient cohort, likely leading to even less risk of excess cardiac mortality. The increased risk of cardiac death observed in patients with pre-existing heart disease, as well as the higher rate in the generally older no-RT group, including 32 of 166 deaths within the first 12 months, highlights the appropriateness of judicious omission of RT in older patients with cardiac comorbidities and low-risk breast cancer.

Bian et al. No acute changes in LVEF observed with concurrent trastuzumab and breast radiation with low heart doses. *Clin Breast Cancer*. In press. (17)

Summary: Bian et al retrospectively evaluated left ventricular ejection fraction (LVEF) in 88 patients with non-metastatic HER2-positive breast cancer who received concurrent trastuzumab and breast or chest wall RT at a single institution between 2008 and 2015 (17). Baseline LVEF before initiation of trastuzumab was compared with: (*1*) LVEF after completion of RT at the time point closest to completion of trastuzumab; and (*2*) lowest posttreatment LVEF within 3 years of completion of RT. A 2-way analysis of variance was used to look at effect of laterality and doxorubicin treatment. Linear regression models were used to examine the relationship of cardiac RT dose and LVEF changes. There were 41 right breast and 45 left breast patients. Sixty-one patients (31 right breast, 30 left breast) received supraclavicular and internal mammary RT. Mean heart dose was 1.10 Gy for right breast patients and 3.63 for left breast patients. At a median follow-up of 45 months they found a 3% decrease in LVEF from before to after treatment across the whole cohort, as well as a significant doxorubicin effect, but no difference between left and right breast patients. A test for interaction of laterality and doxorubicin was not significant. No significant association was found between any heart dose parameter and LVEF change after controlling for doxorubicin use.

Comments: The sequential or concurrent use of systemic therapies that can cause cardiac morbidity complicates the analysis and understanding of RT cardiac toxicity. The concurrent use of trastuzumab and RT is particularly common: approximately 25% of breast cancers are Her-2 amplified. Existing data suggest that concurrent treatment is safe (18-23). In this study, Bian et al look at LVEF as a potential early marker of subclinical cardiac damage and specifically whether addition of RT increases acute changes. One potential benefit of the use of LVEF as a tool is that serial measurements are already standard of care in these patients. The idea of an acute indicator of cardiac injury to identify patients who should therefore perhaps be followed more closely or considered for medical or procedural interventions, rather than waiting for a cardiac event to develop, is an interesting one. Ultimately, however, there was no difference seen between left- and right-sided patients, consistent with prior safety data. The small sample size of this single-institution study does limit the conclusions that can be drawn, particularly given the overall low rate of cardiac events seen in more modern series. As prospective trastuzumab clinical trial data mature, we will get longer-term data. However, the currently existing data strongly suggest that concurrent treatment with breast RT is safe, particularly with low MHDs that should be achievable in most centers with modern techniques.

Our understanding of the relationship between RT for breast cancer and subsequent cardiac risk is evolving. We have increasing data that lower heart doses are afforded by modern treatment techniques and that this results in lower than previously observed cardiac toxicity, including no discernable difference in cardiac mortality with left-sided treatment. The validation of a predictive model for ACEs with the suggestion of LV-V5 as a potentially useful predictive dose parameter, instead of or in addition to MHD, suggests an important avenue for future study. Although we cannot randomize patients to more or less cardiac dose, creative analysis of existing randomized trial data may allow estimation of excess RRs by cardiac dose. There are increasing data that concurrent use of the highly effective drug trastuzumab with breast/chest wall RT in patients with HER-2 amplified breast cancer is safe. Finally, the data discussed here confirm the impact of patient-specific factors, particularly smoking and pre-existing cardiac disease, on subsequent cardiac risk, highlighting the importance of

individualized risk-benefit assessment when making breast RT decisions.

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