Letter to the Editor

Radiation for Prior DCIS is a Risk Factor for Death From Invasive Breast Cancer

Re: Li PC, Zhang Z, Cronin AM, Punglia RS. Mortality After Invasive Second Breast Cancers Following Prior Radiotherapy for DCIS. *J Natl Compr Canc Netw* 2019;17(11):1367–1371.

We read with interest the article by Li et al¹ regarding the impact of prior radiotherapy (RT) for ductal carcinoma in situ (DCIS) on the prognosis of women with invasive breast cancer. The authors report that the risk of breast cancer mortality following invasive breast cancer among women with a prior diagnosis of DCIS is 1.7 times higher if the DCIS was treated with lumpectomy + RT versus lumpectomy alone (adjusted hazard ratio [HR], 1.70; 95% CI, 1.18–2.45; $P=.005$). The authors suggest that this finding may have implications for the use of RT in the initial treatment of DCIS. However, we propose another interpretation.

Treatment of DCIS with lumpectomy + RT, compared with lumpectomy alone, is associated with a large reduction in the risk of subsequent ipsilateral invasive breast cancer but little or no reduction in the risk of breast cancer mortality.^{2,3} In SEER, we compared the risks of ipsilateral invasive recurrence and of breast cancer–specific mortality among patients

with DCIS treated with lumpectomy ± RT using one-to-one matching.² In this analysis (including 29,465 propensity-matched pairs of patients), the use of RT after lumpectomy was associated with a 36% reduction in the 15-year risk of ipsilateral invasive breast cancer (8.1% vs 5.2%; absolute reduction of 2.9%) and a small reduction in the risk of breast cancer mortality (2.0% vs. 1.8%; absolute reduction of 0.2%). The ratio of deaths to recurrences increased from 0.25 in patients treated with lumpectomy alone to 0.35 in patients treated with lumpectomy + RT; therefore, for every 10,000 patients treated with lumpectomy alone, we would expect approximately 810 ipsilateral invasive recurrences and 200 breast cancer deaths, whereas for every 10,000 patients treated with lumpectomy + RT, we would expect 520 ipsilateral invasive recurrences and 180 breast cancer deaths. These numbers correspond to a HR for death associated with RT of approximately 1.40, suggesting that the HR of 1.70 generated by Li et al¹ may in part be explained by a reduction in the number of cases (ie, patients with recurrence after DCIS) but no reduction in the number of deaths.

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Author's Reply

to Letters to the Editor by Ding and Li, and Sopik, Giannakeas, and Narod

We would like to thank the contributors for their letters regarding our manuscript in the November 2019 issue of *JNCCN*,¹ and would like to thank the editors for the opportunity to respond to their comments and facilitate further discussion on the topic of radiotherapy (RT) for ductal carcinoma in situ (DCIS) and breast cancer–specific mortality after invasive breast recurrence.

In the first letter, Ding and Li² performed a comparable analysis with the addition of a more in-depth comparison of clinicopathologic factors in the initial breast-conserving surgery (BCS) alone and BCS + RT groups, and used inverse probability propensity score weighting to balance patient characteristics between the groups. They similarly found prior RT to be associated with higher breast cancer–specific mortality in patients with ipsilateral second breast cancer (SBC; 95% vs 88%), but not contralateral SBC (92% vs 94%). In their multivariable competing risk model adjusting for age at

diagnosis, year of diagnosis, estrogen receptor status, progesterone receptor status, nuclear grade, race/ethnicity, marital status, receipt of chemotherapy, and disease stage, the overall hazard ratio (HR) for prior RT was 1.34 (95% CI, 1.06–1.69; $P=.014$), with an association by laterality of SBC.

We agree with Ding and Li's statement that patient characteristics of the BCS alone and BCS + RT groups are expected to be imbalanced, and showed the differences in Table 1 of our manuscript. We discussed in our manuscript our decision to examine outcomes after SBC rather than after initial treatment, and compare ipsilateral and contralateral SBCs to mitigate the effects of selection bias and consequent differences. Additionally, we used a multivariable regression analysis including the known imbalanced characteristics to help account for these imbalances. We appreciate Ding and Li's effort to balance the differences using propensity score weighting and

their support of the same conclusion: that patients previously received RT for DCIS had higher mortality after developing ipsilateral SBC than those who did not receive RT. Furthermore, our shared conclusion is supported by the randomized clinical trial data on RT for DCIS and the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, which reported a slightly higher risk of mortality in women who were allocated to RT.³

In the second letter, Sopik, Giannakeas, and Narod⁴ propose that rather than increasing mortality after an invasive SBC, prior RT for DCIS only appears to do so due to the mathematical consequence of reducing the number of recurrences with minimal reduction in the number of breast cancer deaths.

We agree that the main reason for our finding is that in the equation for mortality after invasive recurrence there is a decrease in the denominator (ie, number of recurrences) rather than a change in the

numerator (ie, number of deaths). With our study, we start to address the longstanding question of *why*, unlike for early-stage invasive breast cancer, reducing invasive breast cancer recurrence with adjuvant RT for DCIS does not translate into a reduction in breast cancer mortality.⁵ In other words, why does the numerator not decrease proportionally? We suggest a few possible explanations in our manuscript. One is that prior RT limits subsequent salvage options; a smaller proportion of patients with ipsilateral SBC received RT than those with contralateral SBC in this cohort. Another is the possibility that RT may be less effective in treating biologically more aggressive disease which, once it recurs, could be associated with higher mortality. Indeed, in our analysis, compared with women who underwent BCS alone, those who developed an invasive recurrence and had received RT for DCIS were younger at the time of recurrence and had breast cancers that were more likely to lack estrogen receptor expression, characteristics that are associated

with more aggressive cancer biology. Additionally, the minimal effect of RT on breast cancer mortality after invasive breast cancer in the contralateral breast supports one or both of these explanations.

Ultimately, a retrospective, SEER-based analysis is merely hypothesis-generating, and cannot provide a definitive answer as to the impact of RT on mortality after an invasive cancer recurrence. However, a sufficiently powered randomized clinical trial investigating this question is not possible to conduct. In this context, we feel that our study provides a compelling case for the importance of careful discussion during DCIS treatment decision-making.

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