Letter to the Editor

Re: "Mortality After Invasive Second Breast Cancers Following Prior Radiotherapy for DCIS"

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.

The recent article by Li et al¹ reports that patients who previously received radiotherapy (RT) for DCIS had higher mortality after developing an invasive second breast cancer (SBC) than those who did not receive RT. This analysis, based on analysis of the SEER database, included 3,407 patients who received breast-conserving surgery (BCS) ± RT for primary ductal carcinoma in situ (DCIS) in 2000 through 2013 and subsequently developed a stage I–III invasive SBC within the same period. Fine-Gray competing risk models were used to study the association between receipt of RT and mortality after SBC. As a retrospective study, the author points out that there are many limitations of this study, such as surgical margin status, use of endocrine therapy, patient comorbidities, reasons for treatment selection, and use of salvage therapy not reported in the SEER database, that may have influenced overall results. However, an obvious deficiency is that patient characteristics between BCS alone and BCS + RT groups were imbalanced, which will affect the reliability of the results.

For this reason, we attempted to reanalyze the study. A dataset of patients who had prior DCIS and developed a subsequent breast cancer was constructed by implementing the MP-SIR session of the SEER*Stat software. Using Li et al's inclusion and exclusion criteria, we identified 1,938 patients who received BCS ± RT for primary DCIS in 2000 through 2013 and subsequently developed a stage I–III invasive SBC within the same time period. We used the same statistical analytic approach as reported in an earlier study that examined the benefit of breast surgery for DCIS,² and compared clinicopathologic factors between BCS alone and BCS + RT groups using Pearson or Mantel-Haenszel chi-square tests for categorical and ordinal factors, respectively. For inferring missing values of marital status ($n=81$; 4.2%), nuclear grade ($n=404$; 20.8%), estrogen receptor (ER) status ($n=1,078$; 55.6%), and progesterone receptor

(PgR) status ($n=1,128$; 58.2%), we applied a multiple imputation procedure with the following variables: patient age (continuous), race (white, black, other), nuclear grade (I, II, III), receipt of chemotherapy, year of diagnosis, breast cancer stage, and SBC laterality (ipsilateral, contralateral). To stabilize the results, the procedure was repeated for 10 cycles to produce a single imputed dataset.

We then used inverse probability propensity score weighting to balance patient characteristics between the BCS alone and BCS + RT groups. To calculate propensity scores, baseline characteristics of laterality of SBC, patient age, year of diagnosis (categorical, 10-year intervals), marital status, race/ethnicity, ER status, PgR status, nuclear grade, SBC stage, and receipt of chemotherapy were applied to a logistic regression model for receipt of RT (Table 1).

We compared SBC in the BCS alone and BCS + RT groups using propensity score-weighted log-rank tests and Cox proportional hazards models. Hazard ratios (HRs) of BCS were reported from multivariable models that adjusted for patient age, year of diagnosis, race/ethnicity, marital status, ER status, PgR status, nuclear grade, SBC stage, and receipt of chemotherapy. Interaction tests were performed to explore whether any survival benefit conferred by RT varied across subgroups. All P values were derived from 2-sided t tests that used $\alpha=.05$ to assess statistical significance. Statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing).

We identified a total of 143 deaths due to breast cancer in the cohort: 65 among patients receiving BCS alone and 78 among those receiving BCS + RT for primary DCIS. Another 185 deaths were attributed to other causes (113 among patients receiving BCS alone and 72 among those receiving BCS + RT for primary DCIS). Median follow-up for survivors from time of SBC diagnosis was 65 months (interquartile range, 34–100 months).

In our analysis, the 5-year cumulative incidence of breast cancer-specific survival after development of ipsilateral SBC was significantly higher in women who received no prior RT versus prior RT (95.0% vs 88.4%;

supplemental eFigure 1A, available with this article at JNCCN.org), whereas there was no difference among those who developed contralateral SBC (92.0% vs 94.2%; supplemental eFigure 1B). In a multivariable competing risk analysis adjusting for age, year of diagnosis, race/ethnicity, marital status, ER status, PgR status, nuclear grade, receipt of chemotherapy, and SBC stage, no prior RT in the treatment of primary breast cancer remained significantly associated with increased cancer-specific survival (HR, 1.34; 95% CI, 1.06–1.69; $P=.014$). Interaction analysis suggested that this association differed by laterality of SBC (ipsilateral: HR, 2.05; 95% CI, 1.47–2.85; $P<.001$ vs contralateral: HR, 0.82; 95% CI, 0.58–1.15; $P=.251$; $P_{\text{interaction}}<.001$). Factors independently associated with breast cancer-specific survival after SBC included age at SBC diagnosis ($P=.004$), race ($P<.001$), receipt of chemotherapy ($P<.001$), PgR status ($P=.025$), and SBC stage ($P<.001$), although not associated with ER status ($P=.461$).

Results of our study are roughly same as the original study: patients who previously received RT for DCIS had higher mortality after developing ipsilateral SBC than those who did not receive RT. However, results of this study are more convincing after balancing patient baseline characteristics.

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doi: 10.6004/jnccn.2020.7530

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1. 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;17:1367–1371.
2. Sagara Y, Freedman RA, Vaz-Luis I, et al. Patient prognostic score and associations with survival improvement offered by radiotherapy after breast-conserving surgery for ductal carcinoma in situ: a population-based longitudinal cohort study. *J Clin Oncol* 2016;34:1190–1196.

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Table 1. Patient Characteristics by Treatment of Primary Ductal Carcinoma In Situ

Characteristic	Unmatched Cohort		P Value	Matched Cohort	
	BCS Alone n (%)	BCS + RT n (%)		BCS Alone n (%)	BCS + RT n (%)
Total, N	906	1,032		906	1,032
Laterality of SBC			<.001		
Ipsilateral	524 (58)	443 (43)		442 (48.8)	509 (49.3)
Contralateral	382 (42)	589 (57)		464 (51.2)	522 (50.7)
Age, y			<.001		
40–49	200 (22)	266 (26)		245 (27.0)	240 (23.3)
50–59	239 (26)	320 (31)		259 (28.6)	305 (29.6)
60–69	229 (25)	289 (28)		214 (23.6)	297 (28.8)
70–79	167 (18)	129 (12)		138 (15.2)	152 (14.7)
≥80	71 (8)	28 (3)		51 (5.6)	35 (3.4)
Year of diagnosis			.014		
2000–2002	362 (40)	365 (35)		345 (38.1)	387 (37.5)
2003–2005	253 (28)	301 (29)		265 (29.3)	298 (28.9)
2006–2008	172 (19)	207 (20)		176 (19.4)	198 (19.2)
2009–2011	83 (9)	133 (13)		83 (9.2)	124 (12.0)
2012–2013	36 (4)	26 (3)		37 (4.0)	24 (2.4)
Race/Ethnicity			.561		
White	715 (79)	815 (79)		710 (78.4)	814 (78.9)
Black	120 (13)	125 (12)		122 (13.5)	129 (12.5)
Other ^a	71 (8)	92 (9)		73 (8.1)	89 (8.6)
Marital status			.005		
Single	519 (57)	666 (65)		545 (60.1)	640 (62.0)
Separated	130 (14)	120 (12)		140 (15.4)	115 (11.2)
Married	257 (28)	246 (24)		223 (24.6)	277 (26.8)
Estrogen receptor status			.005		
Negative	102 (11)	163 (16)		131 (14.5)	143 (13.9)
Positive	804 (89)	869 (84)		774 (85.5)	889 (86.1)
Progesterone receptor status			.057		
Negative	209 (23)	278 (27)		234 (25.8)	260 (25.2)
Positive	697 (77)	754 (73)		672 (74.2)	772 (74.8)
Nuclear grade			<.001		
I	170 (19)	136 (13)		138 (15.2)	163 (15.8)
II	389 (43)	400 (39)		371 (40.9)	414 (40.1)
III	347 (38)	496 (48)		398 (43.9)	454 (44.0)
SBC stage			.495		
I	584 (64)	690 (67)		595 (65.7)	674 (65.3)
II	249 (27)	269 (26)		244 (26.9)	279 (27.0)
III	73 (8)	73 (7)		67 (7.4)	79 (7.7)
Receipt of chemotherapy			.013		
No	901 (99)	1,012 (98)		889 (98.1)	1,018 (98.6)
Yes	5 (1)	20 (2)		16 (1.8)	14 (1.4)
Median interval from primary to SBC (interquartile range), mo					
BCS alone	61.0 (29.3–95.0)				
BCS + RT	68.0 (37–104)				

Abbreviations: BCS, breast-conserving surgery; RT, radiotherapy; SBC, second breast cancer.

^aIncluding American Indian/Alaskan Native, Asian/Pacific Islander.

Supplemental online content for:

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J Natl Compr Canc Netw 2020;18(5):xl–xlii

eFigure 1: Cumulative Incidence of BC-Specific Survival

eFigure 1. Cumulative incidence of BC-specific survival after an (A) ipsilateral or (B) contralateral stage I–III second BC in patients receiving breast-conserving surgery for primary ductal carcinoma in situ. Abbreviations: BC, breast cancer; RT, radiotherapy.