Older Patients With Early-stage Breast Cancer

Adjuvant Radiation Therapy and Predictive Factors for Cancer-related Death

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Purpose: Studies have shown that older women are undertreated for breast cancer. Few data are available on cancer-related death in elderly women aged 70 years and older with pathologic stage T1a-b N0 breast cancer and the impact of prognostic factors on cancer-related death.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was queried for women aged 70 years or above diagnosed with pT1a or pT1b, N0 breast cancer who underwent breast conservation surgery from 1999 to 2003. The Kaplan-Meier survival analysis was performed to evaluate breast cause-specific survival (CSS) and overall survival (OS), and the log-rank test was employed to compare CSS/OS between different groups of interest. Multivariable analysis (MVA), using Cox proportional hazards regression analysis, was performed to evaluate the independent effect of age, race, stage, grade, ER status, and radiation treatment on CSS. Adjusted hazard ratios were calculated from the MVA and reflect the increased risk of breast cancer death. Competing-risks survival regression was also performed to adjust the univariate and multivariable CSS hazard ratios for the competing event of death due to causes other than breast cancer.

Results: Patients aged 85 and above had a greater risk of breast cancer death compared with patients aged 70 to 74 years (referent category) (adjusted hazard ratio [HRs] = 1.98). Race had no effect on CSS. Patients with stage T1bN0 breast cancer had a greater risk of breast cancer death compared with stage T1aN0 patients (adjusted HR = 1.35; $P = 0.09$). ER negative patients had a greater risk of breast cancer death compared with ER positive patients (adjusted HR = 1.59; $P < 0.017$). Patients with higher grade tumors had a greater risk of breast cancer death compared with patients with grade 1 tumors (referent category) (adjusted HRs = 1.69 and 2.96 for grade 2 and 3, respectively). Patients who underwent radiation therapy had a lower risk of breast cancer death compared with patients who did not (adjusted HR = 0.55; $P < 0.0001$).

Conclusions: Older patients with higher grade, pT1b, ER-negative breast cancer had increased risk of breast cancer-related death. Adjuvant radiation therapy may provide a CSS benefit in this elderly patient population.

Key Words: radiation, elderly, survival, breast

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The elderly population in the United States continues to increase. As suggested by US consensus data, the number of people who were 65 years and older in the United States reached 40.3 million on April 1, 2010, up from 31.2 million in 1990 to 35.0 million in 2000.[1] According to the Surveillance Epidemiology and End Results (SEER) database, from 2005 to 2009 approximately 41% of patients with breast cancer were diagnosed above the age of 65 years, of which 21% were above the age of 75 years. Breast cancer related deaths during this time period was 57.4% for patients above the age of 65 years, of which 37.5% were above the age of 75 years. Furthermore, annually 40,000 women aged 70 years or above in the United States will be diagnosed with tumors no greater than 2 cm in size.[2]

Despite an increase in the incidence of breast cancer in elderly population, the optimal management of breast cancer in the elderly population is unclear.[2] Clinical treatment decisions are based individually on tumor characteristics and treatment side effects against patients' health status, comorbidities, and life expectancy.[3] There is low enrollment of patients aged 65 years and older in randomized clinical trials.[4–6] Concern that treatment guidelines based on studies in younger patients may not be applicable to elderly patients may lead to elderly patients being undertreated.[7,8] Two randomized trials have called into the question the need for adjuvant radiation after breast conservation surgery (BCS) in the elderly population.[9,10] On the basis of the results from these studies, the NCCN guidelines has incorporated lumpectomy alone as a treatment option in patients aged 70 years and older diagnosed with T1 tumors that are node negative and estrogen receptor (ER) positive and are able to take the adjuvant hormone therapy for 5 years.

There is lack of literature regarding the various decision-making factors that are considered to omit adjuvant radiation in low-risk, older breast cancer patients. The overall treatment recommendations should take into consideration the patient's life expectancy and comorbidities.

The purpose of this study was to determine the role of radiation therapy (RT) on breast cancer cause-specific survival (CSS) for elderly female patients, age 70 years and above with early-stage breast cancer by analyzing the SEER database. To better tailor therapy for individual patient, a secondary goal of this study is to identify prognostic factors including age, race, grade, hormone receptor status (ER), and use of adjuvant RT on breast cancer-related death.

METHODS

The SEER database was queried for women aged 70 years and above of age diagnosed with pT1a or pT1b, N0 M0 breast cancer that underwent BCS from 1999 to 2003. Patients who were male, aged 70 years or below, tumor size >10 mm, node positive, or underwent brachytherapy were excluded. The cohort was stratified by age, race, stage, grade, ER status, and use of adjuvant radiation.

Descriptive statistics (including mean, SD, median, range, frequency, percentage) were calculated to characterize the study cohort in relation to demographic, prognostic, and treatment factors of interest. The primary endpoint was breast cancer CSS. CSS was ascertained by selecting breast cancer as the cause of death in the SEER database search. Deaths due to causes other than breast cancer were censored when estimating CSS. CSS was defined as the time from diagnosis until death from breast cancer (or until the date of last follow-up or death from other cause).

The Kaplan-Meier survival analysis was performed to evaluate CSS and overall survival (OS), and the log-rank test was employed to compare CSS/OS between different groups of interest. Multivariable analysis (MVA), using Cox proportional hazards regression analysis, was performed to evaluate the independent effect of age, race, stage, grade, ER status, and radiation treatment on CSS. Adjusted hazard ratios (HR) were calculated from the MVA and reflect the increased risk of breast cancer death. Competing-risks survival regression was also performed to adjust the univariate and multivariable CSS HR for the competing event of death due to causes other than breast cancer (based on Fine and Gray's proportional sub hazards model). All P-values are 2-sided with statistical significance evaluated at the 0.05 α-level. Ninety-five percent confidence intervals (CI) for adjusted HR's and sub-HR were calculated to assess the precision of the obtained estimates. All analyses were performed using the SPSS version 22.0 (SPSS Inc., Chicago, IL) and STATA Version 13.0 (StataCorp, College Station, TX).

RESULTS

Patient, Tumor, and Treatment Characteristics

There were 6370 patients who met the inclusion criteria for analysis. There were 2316 (36.4%) patients aged 70 to 74 years, 2190 (34.4%) patients aged 75 to 79 years, 1236 (19.4%) patients aged 80 to 84 years, and 628 (9.9%) patients that were 85 years or older. In the entire cohort, 5851 (91.9%) patients were classified as white, 240 (3.8%) patients were classified as black, and 279 (4.4%) were classified as other. There were 1325 (20.8%) patients with T1a tumors and 5045 (79.2%) patients with T1b tumors. Among all patients, 5862 (92.0%) were ER positive and 508 (8.0%) were ER negative. There were 2854 patients (44.8%) with grade 1 tumors, 2761 (43.3%) patients with grade 2 tumors, and 705 (11.1%) patients with grade 3 tumors. A total of 4460 (70.0%) patients received RT and 1910 (30.0%) patients did not undergo radiation therapy. Table 1 summarizes patient, tumor, and treatment characteristics.

Survival and Competing-risk Adjusted Analysis

A total of 2554 (40.1%) patients died in the cohort. A total of 229 (9.0%) patients died from breast cancer, 121 (4.7%) patients died from lung disease, 121 (4.7%) patients died from heart disease, and 1519 (59.5%) patients died from other causes in this cohort. The CSS among patients aged 70 to 74, 75 to 79, 80 to 84, and 85 years and above was 96.9%, 96.5%, 96.0%, and 94.9%, respectively.

Among the entire cohort, the 100-month OS was 71.5% for patients who underwent radiation and 51.3% for patients who did not receive radiation (HR = 0.50; 95% CI; 0.46-0.54; $P<0.0001$) as seen in Figure 1. The 100-month CSS was 97.0% for patients who underwent radiation and 93.9% for patients who did not receive radiation (HR = 0.53; 95% CI, 0.40-0.68; $P<0.0001$) as seen in Figure 2. The competing-risk adjusted analysis (adjusted for lung, heart, and others causes of death) showed a sub-HR (for radiation vs. no radiation) of 0.63 (95% CI, 0.48-0.82; $P=0.001$) and lung and heart-related deaths were not higher in the radiation group as seen in Table 2.

TABLE 1. Patient, Tumor, and Treatment Characteristics

Characteristics	Number of Patients (%)
Age (y)	
70-74	2316 (36.4)
75-79	2190 (34.4)
80-84	1236 (19.4)
85 +	628 (9.9)
Race	
White	5851 (91.9)
Black	240 (3.8)
Other	279 (4.4)
Stage	
T1a	1325 (20.8)
T1b	5045 (79.2)
ER status	
Positive	5862 (92.0)
Negative	508 (8.0)
Grade	
Grade 1	2854 (44.8)
Grade 2	2761 (43.3)
Grade 3	705 (11.1)
Radiation therapy	
Yes	4460 (70.0)
No	1910 (30.0)

Multivariable Analysis

Patients aged 80 to 84 years demonstrated a trend and patients aged 85 years and greater showed a significantly greater risk of breast cancer death compared with patients aged 70 to 74 (referent category) (adjusted HR's = 1.417 [95% CI,

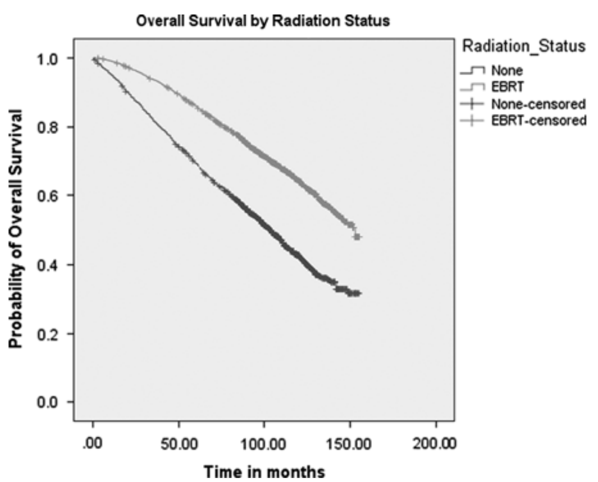

FIGURE 1. The Kaplan-Meier survival curve of overall survival (OS) for the entire cohort. Patients were stratified by whether they received radiation therapy (+radiation therapy; n = 4460 patients) or not (no radiation therapy; n = 1910 patients). Statistical comparison between the survival curves was made using the log-rank test ($P<0.0001$).

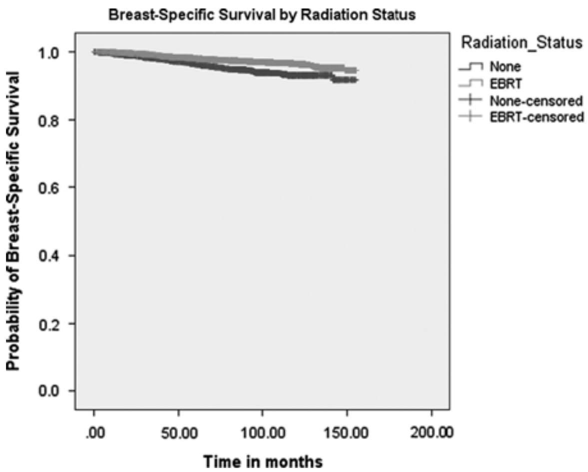

FIGURE 2. The Kaplan-Meier survival curve of CSS for the entire cohort. Patients were stratified by whether they received radiation therapy (+radiation therapy; n=4460 patients) or not (no radiation therapy; n=1910 patients). Statistical comparison between the survival curves was made using the log-rank test ($P<0.0001$).

0.978-2.053]; $P=0.065$, and 1.977 [95% CI, 1.227-3.061]; $P=0.002$ for 80 to 84 and 85 and above age groups, respectively). Patients with T1b tumors had a nonsignificant greater risk of breast cancer death compared with patients with T1a tumors (adjusted HR=1.354 [95% CI, 0.954-1.921]; $P=0.09$). ER-negative patients had a greater risk of breast cancer death compared with ER positive patients (adjusted HR=1.588 [95% CI, 1.086-2.320]; $P=0.017$). Patients with higher grade tumors had a greater risk of breast cancer death compared with patients with grade 1 tumors (referent category) (adjusted HRs=1.693 [95% CI:, 1.239-2.314]; $P=0.001$ and 2.960 [95% CI, 2.004-4.373]; $P<0.0001$, for grade 2 and 3, respectively). Patients who received RT had a lower risk of breast cancer death compared with patients who did not (adjusted HR=0.554 [95% CI, 0.419-0.733]; $P<0.0001$). Race had no effect on CSS when included in the MVA (Table 3).

Adjustment for competing risk of noncancer death altered the HR in the multivariable model as follows. Patients aged 80 to 84 years no longer demonstrated a trend and patients aged 85 years and greater no longer showed a significantly greater risk of breast cancer death compared with patients aged 70 to 74 years (referent category) (adjusted SHR's=1.188 [95% CI, 0.816-1.730]; $P=0.368$ and 1.414 [95% CI, 0.912-2.191]; $P=0.121$ for 80 to 84 years and 85 and above age groups, respectively). Patients with T1b tumors had a nonsignificant greater risk of breast cancer death compared with patients with T1a tumors (adjusted SHR=1.320 [95% CI, 0.932-1.869]; $P=0.118$). ER-negative patients had a greater risk of breast cancer death compared with ER-positive patients (adjusted SHR=1.584 [95% CI, 1.093-2.297]; $P=0.015$). Patients with higher grade tumors had a greater risk of breast cancer death compared with patients with grade 1 tumors (referent category) (adjusted SHRs=1.683 [95% CI, 1.232-2.298]; $P=0.001$ and 2.943 [95% CI, 1.996-4.340]; $P<0.0001$, for grade 2 and 3, respectively). Patients who received RT had a lower risk of breast cancer death compared with patients who did not (adjusted SHR=0.635 [95% CI, 0.475-0.848]; $P=0.002$).

Radiation Effect on CSS Stratified by Hormone Receptor Status and Stage

There was an improvement in the 100-month CSS for patients with ER-positive tumors who underwent RT: 97.3% versus 93.0% (HR=0.52 [95% CI, 0.39-0.69]; $P<0.0001$) as seen in Figure 3. The sub-HR was 0.63 (95% CI, 0.47-0.83; $P=0.001$) when CSS was adjusted for competing risk of noncancer death. There was a trend in improved 100-month CSS for patients with ER-negative tumors who underwent RT: 93.0% versus 88.7% (HR=0.56 [95% CI, 0.29-1.07]; $P<0.08$) as seen in Figure 4. The sub-HR was 0.64 (95% CI, 0.34-1.23; $P=0.18$) when CSS was adjusted for competing risk of noncancer death.

There was an improvement in the 100-month CSS for patients with T1b, ER-positive tumors who underwent RT: 97.1% versus 95.4% (HR=0.51 [95% CI, 0.37-0.70]; $P<0.0001$). There was a trend in improved 100-month CSS for patients with T1a, ER-positive tumors who underwent RT: 97.9% versus 96.4% (HR=0.52 [95% CI, 0.26-1.04]; $P=0.06$).

DISCUSSION

Several randomized studies have shown improved local control with the addition of RT after breast conserving surgery making it the standard of care for patients with breast cancer who want to avoid mastectomy.[11] The addition of tamoxifen further improves the local control benefit for tumors that are 1 cm or less.[12] The results of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Oxford meta-analysis concluded that 1 breast cancer death could be avoided for every 4 local recurrences prevented over 15 years with a 15-year breast cancer mortality risk reduction of 5.4% with the addition of adjuvant RT.[13] Thus, it is reasonable to postulate that improved local control will translate into improved breast cancer-free survival in elderly patients. Treatment of the elderly population with breast cancer who share the same tumor characteristics of younger patients is not straightforward. Women aged 80 years or older are reported to have breast cancer characteristics similar to those of younger women, yet receive less aggressive treatment and experience higher mortality from early-stage breast cancer.[14] It has also been reported that as patients over 70 years of age develop biologically less aggressive tumors and have a shorter time at risk

TABLE 2. Cause of Death Stratified by Radiation Treatment

	Cause of Death (%)					
	Alive	Breast	Lung	Heart	Other	Total
No radiation	871 (45.6)	92 (4.8)	40 (2.1)	288 (15.1)	619 (62.4)	1910
Radiation	2945 (66.0)	137 (3.1)	81 (1.8)	397 (8.9)	900 (20.2)	4460
Total	3816 (59.9)	229 (3.6)	121 (1.9)	685 (10.8)	1519 (23.8)	6370

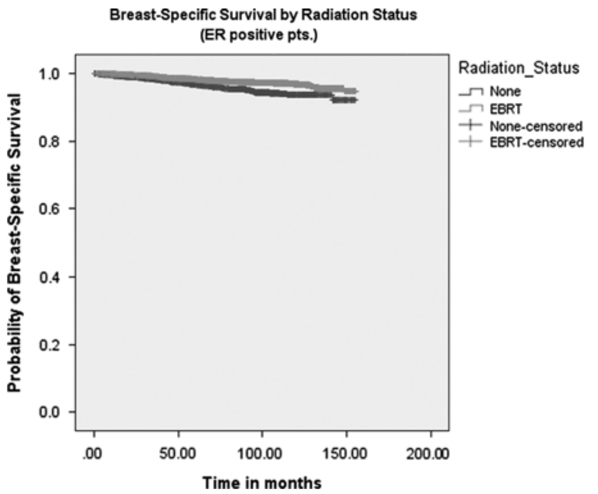

FIGURE 3. The Kaplan-Meier survival curve of CSS for the ER-positive patients. Patients were stratified by whether they received radiation therapy (+radiation therapy; n=4105 patients) or not (no radiation therapy; n=1757 patients). Statistical comparison between the survival curves was made using the log-rank test ($P<0.0001$).

for recurrence than younger women, these benefits may not be seen and less adjuvant treatment may be necessary.[15]

A cause-specific survival benefit was not expected in a relatively low-risk elderly patient population with T1N0 breast cancer treated with adjuvant RT. However, the results of this large study using the SEER database suggest a CSS benefit with the addition of adjuvant RT for elderly patients with early-stage breast cancer. Patients who underwent adjuvant RT had a decreased risk of breast cancer death compared with patients who did not (adjusted HR=0.53; $P<0.0001$) similar to the Oxford meta-analysis. Moreover, when CSS was adjusted for competing risk of noncancer death, lung, heart, and other causes of death were not higher in patients who received RT. The landmark article by Darby and colleagues reported that exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease.[16] This study also included women who underwent RT for breast cancer between 1958 and 2001. The present study included women in the era of RT beginning in 1999 where computed tomography based planning is widely used to decrease radiation dose to normal tissue. Although longer follow-up may be necessary, one could speculate that the improved CSS adjusted for competing risk of death from cardiac causes may be likely due to improved RT planning, delivery, and quality assurance.

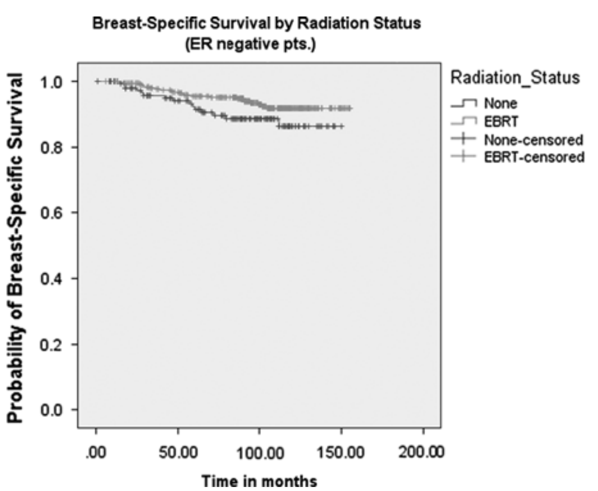

FIGURE 4. The Kaplan-Meier survival curve of CSS for the ER-negative Patients. Patients were stratified by whether they received radiation therapy (+radiation therapy; n=355 patients) or not (no radiation therapy; n=153 patients). Statistical comparison between the survival curves was made using the log-rank test ($P<0.08$).

The NCCN guidelines state that radiation may be omitted in patients that are 70 years of age or older with ER positive, clinically node negative, T1 tumors who receive adjuvant endocrine therapy. Interestingly, this analysis demonstrated that this subgroup may stand to benefit from adjuvant RT with a statistically significant improvement in the CSS for patients with ER-positive tumors who underwent RT that remained after adjusting for competing risks. As mentioned earlier, among the entire cohort, the 100-month OS was 71.5% for patients that underwent RT. This suggests that the majority of women 70 years of age and older who are healthy enough to undergo detection and receive BCS with T1N0 disease are alive at 8 years and may be affected by breast cancer recurrence.

Two randomized trials have studied the omission of RT in the elderly population. Fyles and colleagues reported on a Canadian trial that showed a 7% absolute local control detriment at 5-year follow-up, which increased to 14% at 8-year follow-up with tamoxifen alone compared with tamoxifen and radiation in patients aged 50 years or above with T1-2 tumors after BCS. Although this study included a younger population and larger tumors than the present SEER analysis, approximately 40% of their cohort was aged 70 years and above and 35% of patients had tumors ≤ 1 cm. Furthermore, a planned subgroup analysis of women with T1, hormone-positive tumors indicated a local benefit from RT of 5.5% compared with tamoxifen alone.[9] Hughes and colleagues reported on a stricter group of patients in a Cancer and Leukemia Group B (CALGB) trial who were aged 70 years and above with T1, estrogen-positive tumors after BCS. The absolute local control benefit at 5-year follow-up was only 3%, which increased to 6% at 8-year follow-up and 8% at 12-year follow-up with adjuvant radiation compared with tamoxifen alone.[10]

Results from both trials did not demonstrate a difference in time to distant metastasis, breast cancer-specific survival, or OS with the addition of radiation to tamoxifen.[9,10] However, with the long natural history of breast cancer and median follow-up of approximately 5 years in both trials, an underestimate of the final difference between therapies could exist. For example, in the NSABP B-06 trial, 19% of local relapses after lumpectomy alone occurred 5 to 10 years after treatment, and a further 9% occurred after 10 years.[17] As previously mentioned, the local relapse rate increased 7% and 3% between the 2 arms with an additional 3 years of follow-up in the Canadian and CALGB trials, respectively.[9,10] These numbers are likely to increase as more than half of all recurrences occur between 6 and 15 years after diagnosis for women treated with tamoxifen for 5 years.[18] As such, a survival benefit may be seen in the adjuvant radiation arm similar to our results as improvement in locoregional control is likely to increase subsequent survival.[13]

In addition, the Canadian trial showed an improved absolute 5-year disease-free survival rate of 7% among patients that received radiation in addition to tamoxifen, which was not

TABLE 3. Multivariable Cox Regression Model for Predictors of Breast Cancer Cause-specific Survival

Variables	Adjusted HR	95.0% CI for HR	*P*
RT (referent = no RT)	0.554	0.419-0.733	< 0.0001
Age (referent = 70-74 y)			
75-79	1.197	0.867-1.654	0.274
80-84	1.417	0.978-2.053	0.065
85 +	1.977	1.277-3.061	0.002
Race (referent = white)			
Black	1.084	0.574-2.050	0.803
Other	1.083	0.553-2.120	0.816
Stage T1b (referent = stage T1a)	1.354	0.954-1.921	0.090
ER negative (referent = ER positive)	1.588	1.086-2.230	0.017
Grade (referent = grade 1)			
Grade 2	1.693	1.239-2.314	0.001
Grade 3	2.960	2.004-4.373	< 0.0001

an end point for the CALGB trial. The EBCTCG concluded that differences in disease-free survival in the adjuvant setting often lead to differences in OS with prolonged follow-up.[19] The results of this our study, which had 6370 patients with sufficient follow-up available for analysis, showed a CSS benefit with the addition of radiotherapy. Our results suggest that with further follow-up, the improvement in local control and disease-free survival from adjuvant radiation seen in these trials will translate into a cause-specific survival benefit.

Patients with ER-negative tumors are thought to be the subset of patients who stand to benefit the most from adjuvant RT. Wojcieszynski et al[20] demonstrated that omission of RT in women aged 70 years or above with T1 ER-negative tumors treated with lumpectomy was associated with a 91% increased likelihood of breast cancer mortality in their SEER analysis. This is similar to our findings where ER-negative patients had a greater risk of breast cancer death compared with ER positive patients. Although patients with ER-positive tumors who underwent RT demonstrated a statistically significant improvement in CSS, patients with ER-negative tumors who underwent radiation had a larger absolute improvement in CSS. One could speculate that this did not reach statistical significance secondary to the smaller number of patients in the ER-negative cohort and RT may be of benefit in this group.

There are limitations to this study. Specific clinical and pathologic information such as surgical margin status and use and compliance of endocrine or chemotherapy were not available to further stratify risk categories and may have contributed to selection bias. In addition, as reported by Jagsi et al,[21] adjuvant radiation may be underreported in the SEER database. Women who received radiation may have superior health status, or better access to care overall, or higher socioeconomic status. Further studies using Medicare-SEER database could answer questions related to the role of RT after accounting for pre-existing comorbidities and adjuvant therapies such as endocrine or chemotherapy.

CONCLUSIONS

Older patients with higher grade, pT1b, ER-negative breast cancer had increased risk of breast cancer-related death. Adjuvant RT showed a CSS benefit even in this elderly "low risk" patient population. Although randomized studies could focus on adjuvant treatments that will improve cancer-related death in this age group, it is unlikely that ongoing prospective trials or retrospective data will provide evidence that only one of these options is the best one. This is because of the uniqueness of the risk/benefit ratio for each patient depending on her comorbidities, life expectancy, functional status, treatment priorities, and practical and socioeconomic factors (distance and access to treatment). Therefore, adjuvant RT recommendations should incorporate the above-mentioned factors and not solely rely on the NCCN guidelines to defer RT in this elderly population.

REFERENCES

1. US Census Bureau, Census 2000 Summary File 1 and 2010 Census Summary File 1. Available at: http://www.census.gov/prod/cen2010/briefs/c2010br-09.pdf. Accessed March 14, 2014.
2. Surveillance Epidemiology and End Results (SEER) and National Cancer Institute. Available at:http://seer.cancer.gov/statfacts/html/breast.html#incidence-mortality. Accessed March 14, 2014.
3. Bouchardy C, Rapiti E, Blagojevic S, et al. Older female cancer patients: importance, causes, and consequences of undertreatment. *J Clin Oncol*. 2007;25(no. 14):1858–1869.
4. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer treatment trials. *N Engl J Med*. 1999;341(no. 27):2061–2067.
5. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol*. 2003;21:1383–1389.
6. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol*. 2005;23(no. 13):3112–3124.
7. Malik MK, Tartter PI, Belfer R. Undertreated breast cancer in the elderly. *J Cancer Epidemiol*. 2013;2013:893104.
8. Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the international society of geriatric oncology (SIOG) and European society of breast cancer specialists (EUSOMA). *Lancet*. 2012; 13(no. 4):e148–e160.
9. Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med*. 2004;351:963–970.
10. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med*. 2004;351:971–977.
11. Smith IE, Ross GM. Breast radiotherapy after lumpectomy—no longer always necessary. *N Engl J Med*. 2004;351:1021–1023.
12. Fisher B, Bryant J, Dignam JJ, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *J Clin Oncol*. 2002;20:4141–4149.
13. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;366:2087–2106.
14. Schonberg MA, Marcantonio ER, Li D, et al. Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival. *J Clin Oncol*. 2010;28:2038–2045.

15. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. *J Natl Cancer Inst*. 2000;92:550–556.
16. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368:987–998.
17. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347:1233–1241.
18. Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;378:771–784.
19. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365:1687–1717.
20. Wojcieszynski AP, Shen X, Mishra MV, et al. Radiation and survival in women over 70 with T1 N0 M0 ER-negative breast cancer from 1990 to 2007: a population-based analysis. *J Clin Oncol*. 2011;29(suppl):abstr 1037.
21. Jagsi R, Abrahamse P, Hawley ST, et al. Underascertainment of radiotherapy receipt in Surveillance, Epidemiology, and End Results Registry Data. *Cancer*. 2012;118:333–341.

