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ORIGINAL ARTICLE – BREAST ONCOLOGY

Radiation Therapy After Breast-Conserving Surgery in Women 70 Years of Age and Older: How Wisely Do We Choose?

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ABSTRACT

Background. Despite data from randomized trials supporting omission of radiation therapy (RT) for women ≥ 70 years of age with T1, estrogen receptor-positive (ER+) tumors undergoing breast-conserving therapy (BCT), RT usage remains high. We reviewed our institutional experience to determine if risk factors for local recurrence or comorbidities influenced use.

Methods. Women ≥ 70 years of age with T1, ER+, human epidermal growth factor receptor 2-negative (HER2−) tumors undergoing BCT in 2010–2012 were identified from a prospectively maintained database. Ten-year estimated mortality was calculated using the Suemoto index. The associations of clinicopathological features and mortality risk on receipt of RT were examined.

Results. Overall, 323 patients with 327 cancers were identified. Median age was 75 years, median tumor size was 1 cm, and all were clinically node negative; 53.7% of patients received RT. RT usage decreased with age (73.6%, age 70–74 years; 49.5%, age 75–79 years; 33.3%, age 80–84 years; 10.7%, ≥ 85 years; $p < 0.001$). Within age groups, estimated mortality did not impact RT usage. On multivariable analysis, only younger age and larger tumor size were associated with RT use. Recurrence-free survival was 98% versus 93% with and without RT, respectively ($p = 0.011$). Those who received adjuvant radiation also had improved overall survival (92% vs. 89%), although this effect did not reach statistical significance ($p = 0.051$).

Conclusion. Neither the factors associated with risk of local recurrence nor the estimated risk of death in 10 years were associated with use of adjuvant radiation in a large cohort of women ≥ 70 years of age with small ER+ breast cancers treated with breast-conserving surgery.

A major goal in treating breast cancer is individualization of treatments to optimize local control and prevent recurrence while minimizing morbidity. The widespread adoption of sentinel node biopsy for axillary staging, and the use of genomic testing to decrease chemotherapy utilization in patients with hormonally responsive tumors, are examples of this approach.

Despite attempts to minimize morbidity, radiation therapy (RT) has remained the standard of care for patients undergoing breast-conservation therapy[1–3] based on data from the Early Breast Cancer Trialists' Cooperative Group meta-analyses demonstrating that the reduction in local recurrence associated with the use of RT is associated with an improvement in overall survival (OS). However, this difference did not become apparent until 15 years of follow-up and was only found in women with a > 10% reduction in local recurrence at 5 years.[4]

In selected older women with small (< 2 cm), clinically node-negative, estrogen receptor-positive (ER+) tumors undergoing breast-conserving surgery, the omission of adjuvant RT has been proven to be safe in randomized trials with long-term follow-up.[5–7] While there was a significant difference in local recurrence among patients who did and did not receive adjuvant radiation, this rate was low overall and there was no difference in OS between groups.

Despite these data, a change in the National Comprehensive Cancer Network (NCCN) guidelines,[8] and the 'Choosing Wisely' campaign encouraging cost-effective,

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thoughtful cancer care,[9] the use of radiation in this population of women remains high nationwide.[10,11] We postulated that the decision to use radiation is influenced by both patient and tumor factors in this population of women at low risk of death from breast cancer.

METHODS

Following Institutional Review Board approval of this study, women ≥ 70 years of age with T1 (< 2 cm), ER+, human epidermal growth factor receptor 2-negative (HER2−), clinically node-negative tumors undergoing breast-conserving surgery between 2010 and 2012 were identified from our prospectively maintained service database. ER positivity was defined as > 1% of cells staining positive for ER. Patients with pure in situ carcinoma or previous ipsilateral breast cancers were excluded, and bilateral breast cancers in the same patient were considered as separate events. Clinical, pathologic, treatment, and follow-up data were collected. All patients had an estimated 10-year mortality risk calculated using the Suemoto index.[12] This mortality prediction tool incorporates medical comorbidities, body mass index, lifestyle, functional status, and the patient's assessment of her or his own health to provide an estimate of the risk of mortality in 10 years in patients age > 60 years. The model is based on data from 16 different countries and five different cohorts. As this index is typically calculated prospectively, we utilized a standard institutional patient-completed questionnaire, which was completed at the time of initial surgical consultation to abstract and record information regarding functional status and the patient's own assessment of her or his health.

The primary endpoint of this study was the use of adjuvant radiation. Secondary endpoints included locoregional and distant recurrence as well as OS. Patient and treatment characteristics were summarized using the median and range for continuous variables, and the frequency and percentage for categorical variables. Univariable and multivariable associations with radiation were assessed using mixed-effects models with a random surgeon effect to address the correlation among patients treated by the same surgeon. Factors significantly associated with radiation on univariable analysis were included in multivariable analysis. Kaplan–Meier methods were used to estimate OS and recurrence-free survival (RFS). OS was defined as the time to death from any cause, while RFS was defined as the time to first recurrence. Follow-up time was calculated from the date of surgery, and patients without events at the last follow-up date were censored. A landmark analysis approach was utilized to evaluate the association between radiation, and OS and RFS, with a landmark time of 12 weeks to account for the time from surgery to completion of radiation treatment since exact treatment dates were not always available. Univariable associations with survival and recurrence included a random surgeon effect to account for correlation between patients treated by the same surgeon. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using R Software version 3.4.1 (R Core Development Team, Vienna, Austria).

RESULTS

Overall, 323 patients with 327 cancers met the study inclusion criteria. The median age of the entire cohort was 75 years (range 70–100) at the time of surgery, and the median tumor size was 1 cm. The majority of patients (80.7%) had infiltrating ductal cancers, and invasive lobular carcinoma was present in 11.9%. Forty-eight percent of patients had poorly differentiated tumors, and 15.3% had evidence of lymphovascular invasion. Ten percent of patients had an extensive intraductal component. The median percentage of cells staining positive for estrogen receptor was 95% (Table 1).

Axillary staging was performed in 286 patients (87.4%); 98.6% of patients who had an axillary evaluation underwent sentinel lymph node biopsy (Table 2). Two hundred and seventy-eight patients (96.9%) who underwent axillary staging were node negative, and 11 patients had isolated tumor cells [pN0(i+)]. Most patients (84.7%) began adjuvant endocrine therapy, of whom 155 (56%) lived and were followed for 5 years or longer. Of these 155 patients, 113 (73%) completed at least 5 years of endocrine therapy.

Adjuvant RT was received by 176 (53.8%) patients. Those receiving RT were significantly younger than those who did not (74 vs. 78 years of age, $p < 0.001$). Nearly three-quarters of patients 70–74 years of age (73.6%) were treated with adjuvant radiation, compared with 49.5% of those 75–79 years of age, 33.3% of those 80–84 years of age, and 10.7% of those 85 years of age and older (Fig. 1). Patients treated with adjuvant radiation had a lower estimate of their risk of mortality at 10 years (37% vs. 51%, $p < 0.001$) (Table 1).

Patients receiving adjuvant radiation had larger tumors (1.1 vs. 0.9 cm, $p = 0.026$), and there was no difference in the percentage of poorly differentiated tumors, lymphovascular invasion, or an extensive intraductal component between patients who did and did not receive radiation. Among patients with data available, there was no difference in Oncotype DX (Genomic Health, Redwood City, CA, USA) score based on radiation use (Table 1). Treatment characteristics varied between patients receiving and not receiving RT, with those in the RT group being

TABLE 1 Patient and tumor characteristics

Characteristic	Overall (n = 327)	No radiation (n = 151)	Radiation (n = 176)	p value
Median age at surgery, years (range)	75 (70–100)	78 (70–100)	74 (70–88)	< 0.001
10-year estimate of mortality [% (range)]	43 (22–98)	51 (22–98)	37 (24–96)	< 0.001
Tumor type [n (%)]				0.623[a]
Infiltrating ductal	264 (80.7)	120 (79.5)	144 (81.8)	
Invasive lobular	39 (11.9)	18 (11.9)	21 (11.9)	
Mixed ductal and lobular	4 (1.2)	3 (2.0)	1 (0.6)	
Pure mucinous/colloid/medullary/tubular/papillary	19 (5.8)	9 (6.0)	10 (5.7)	
Other	1 (0.3)	1 (0.7)	0 (0)	
Median tumor size, cm (range)	1 (0.1–2.0)	0.9 (0.1–1.9)	1.1 (0.1–2.0)	0.026
Extensive intraductal component [n (%)]	32 (9.8)	14 (9.3)	18 (10.2)	0.751
Differentiation [n (%)]				0.674
Well differentiated	39 (11.9)	20 (13.2)	19 (10.8)	
Moderately differentiated	91 (27.8)	43 (28.5)	48 (27.3)	
Poorly differentiated	157 (48)	68 (45)	89 (50.6)	
Lymphovascular invasion	50 (15.3)	19 (12.6)	31 (17.6)	0.23
Median percentage of cells positive for ER (%)	95	95	95	
Oncotype DX score (range)	13 (0–40)	14 (3–33)	13 (0–40)	0.693

ER Estrogen receptor

[a]Comparing infiltrating ductal carcinomas with all others

TABLE 2 Treatment characteristics

Treatment characteristic	Overall (n = 327)	No radiation (n = 151)	Radiation (n = 176)	p value
Axillary evaluation				0.434
Axillary lymph node dissection	7 (2.1)	2 (1.3)	5 (2.8)	
Sentinel lymph node biopsy	279 (85.3)	119 (78.8)	160 (90.9)	
None	41 (12.5)	30 (19.9)	11 (6.2)	
Endocrine therapy	277 (84.7)	123 (81.5)	154 (87.5)	0.111
Completion of endocrine therapy	205 (74.0)	88 (71.5)	117 (76)	0.375
Adjuvant chemotherapy	31 (9.5)	5 (3.3)	26 (14.8)	< 0.001
Re-excision	52 (15.9)	15 (9.9)	37 (21.0)	0.002

Data are expressed as n (%)

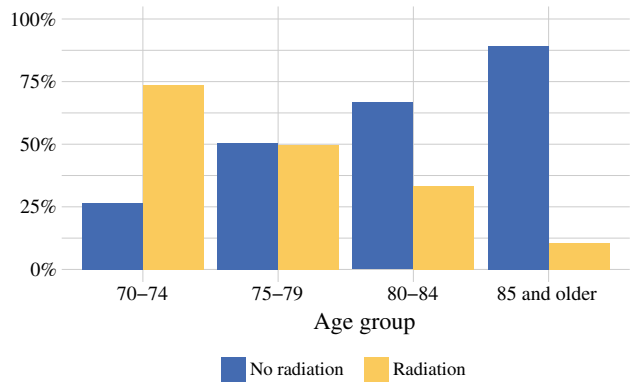

FIG. 1 Adjuvant radiation stratified by age group

significantly more likely to undergo re-excision and to receive chemotherapy (Table 2). Twenty-four patients (7.3%) did not receive adjuvant radiation, chemotherapy, or endocrine therapy (Table 2).

The Suemoto index incorporates age, in 5-year increments, to predict 10-year mortality, and we analyzed age as a continuous variable; therefore, age and Suemoto index have a strong positive association ($p < 0.001$). We evaluated the interaction between continuous age and 10-year risk of mortality on receipt of adjuvant radiation and found no significant effect ($p = 0.112$), suggesting that patients of the same age have the same odds for receipt of radiation regardless of Suemoto index. On multivariable analysis,

increased age was associated with decreased odds of receipt of radiation, and increased tumor size was associated with increased odds of receipt of radiation; whereas the need for one or two re-excisions demonstrated a non-significant increase in odds of radiation ($p = 0.055$), and Suemoto index was not independently associated with receipt of radiation (Table 3).

After a median follow-up of 5.1 years, 36 patients died from any cause, with an overall 5-year survival of 89% (95% confidence interval [CI] 85–93%). Among patients who received adjuvant radiation, 5-year OS was 92% (95% CI 88–97%), versus 85% in those who did not (95% CI 79–92%) (Fig. 2a), although this difference was not statistically significant ($p = 0.051$). Fifteen patients developed a recurrence of their initial cancer, representing a 5-year RFS rate of 95% (95% CI 93–98%). RFS was significantly better among patients who received radiation (98%; 95% CI 95–100%) than among those who did not (93%; 95% CI 88–98%; $p = 0.011$) (Fig. 2b). Fourteen of 15 (93.3%) recurrences were locoregional; there was one distant recurrence without locoregional recurrence. Among the patients who recurred locoregionally, seven had an ipsilateral breast recurrence, five had an ipsilateral axillary recurrence, and two had an ipsilateral breast and axillary recurrence, for a total of nine ipsilateral breast tumor recurrences and seven ipsilateral axillary recurrences. Among patients with an ipsilateral breast tumor recurrence, three had adjuvant radiation and five did not. Furthermore, of patients with an ipsilateral axillary recurrence, two had adjuvant radiation and six did not. Of the seven patients with an ipsilateral axillary recurrence, four underwent axillary surgery (three patients had a sentinel lymph node biopsy and one patient had an axillary lymph node dissection) and three had no surgical axillary evaluation.

Of the seven axillary recurrences, three occurred in patients who took no endocrine therapy. Two refused therapy, and one patient was perceived to have such minimal invasive disease that medication was considered to be optional. One recurrence was in association with a local recurrence. In total, the rate of isolated local recurrence was 3/323 (0.9%).

On univariable analysis, age, tumor size, a higher estimated 10-year mortality risk, and the presence of lymphovascular invasion were significantly associated with recurrence.

TABLE 3 Multivariable analysis of factors associated with receipt of adjuvant radiation

Factor	OR	95% CI	*p* value
Age at surgery	0.38	0.25–1.00	< 0.001
E-prognosis score	0.76	0.52–1.00	0.142
Tumor size	1.52	1.17–2.00	0.002
Number of re-excisions			0.055
0	Ref		
1	2.44	1.14–5.00	
2	2.02	0.11–37.00	

OR Odds ratio, *CI* confidence interval

DISCUSSION

In this study of women ≥ 70 years of age with small ER+ tumors treated by lumpectomy at an academic medical center, the use of adjuvant radiation was 50% overall, and nearly 75% in women 70–75 years of age despite data from randomized controlled trials demonstrating no survival advantage to adjuvant radiation in this population. In the Cancer and Leukemia Group B (CALGB) study of women treated with lumpectomy and tamoxifen, the addition of radiation did not change survival with over 10 years of follow-up (67% vs. 66%) despite a significant difference in locoregional RFS (98% vs. 90% at 10 years).[5,6] Similarly, the PRIME II trial compared patients with tumors up to 3 cm in size and showed no difference in OS at 5 years (93.9% in both groups) despite an absolute difference in ipsilateral breast tumor recurrence of approximately 3% between groups (1.3% vs. 4.1%).[7]

Two retrospective studies demonstrated improved survival when adjuvant radiation was administered in conjunction with endocrine therapy in older women. However, the propensity matching performed did not eliminate the selection biases inherent in retrospective reviews, and their findings should not challenge the results of the prospective randomized trials.[13,14] In fact, a meta-analysis of over 2300 patients, including the two randomized studies, showed that while the addition of radiation to tamoxifen reduced local recurrence from 60 to 10 per 1000 patients at 10 years of follow-up, and reduced axillary recurrence from 12 to 3 per 1000 at 5 years follow-up,[15] there was no difference in distant recurrence or OS.[3,5,7,16]

Although adjuvant radiation was used in approximately half of our study population, its use was notably less than that reported in other large observational series. McCormick and colleagues evaluated changes in practice patterns after the publication of CALGB 9343.[11] In 2009, 5 years after the publication of CALGB 9343, 88% of over 1000 women 70–74 years of age who met the criteria for inclusion in CALGB 9343 identified in the NCCN database were treated with adjuvant radiation, a decrease from 94% in 2000. Usage in this same age group in our study was significantly less, with 75% undergoing RT. The majority of patients received a hypofractionated regimen, thus shortening the time required for treatment. It is unclear

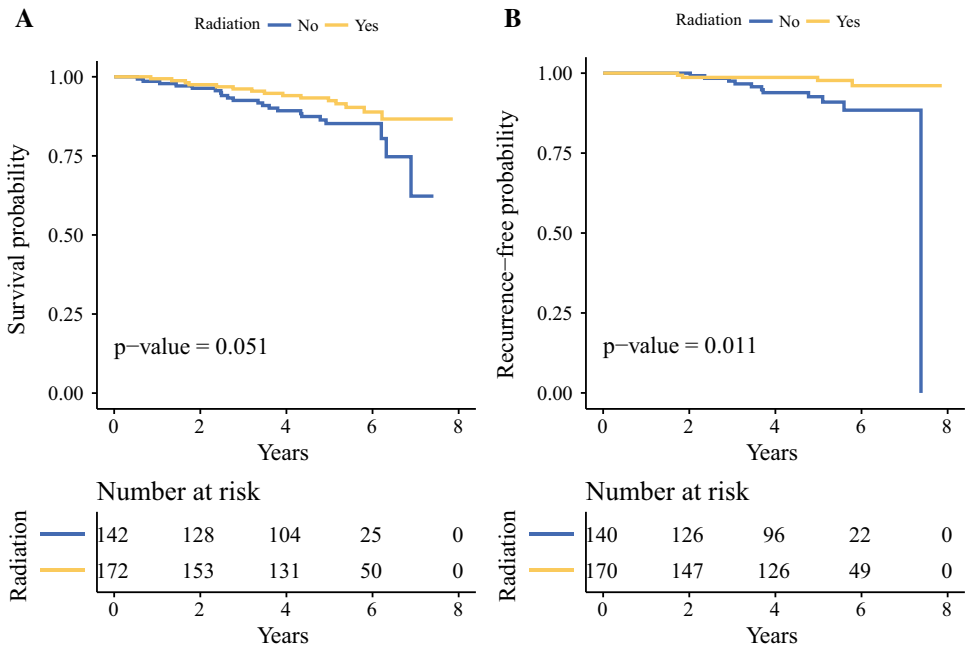

FIG. 2 **a** Overall survival and **b** recurrence-free survival stratified by adjuvant radiation

whether this weighed into the decision for treatment as opposed to observation. Palta et al. evaluated over 40,000 women in the Surveillance, Epidemiology, and End Results (SEER) database and confirmed a similarly small (68.65% to 61.7%) but statistically significant decline in the use of adjuvant radiation in women over 70 years of age after publication of CALGB 9343.[10] Our decreased usage when compared with national rates is perhaps a reflection of the increased acceptance and adoption of the data supporting its omission in this patient population.

Similar to the findings of McCormick et al., we found the use of RT was strongly related to age. Approximately 75% of women 70–75 years of age received adjuvant radiation, compared with fewer than 10% of women older than 85 years of age in our study. Using NCCN data, McCormick et al. also showed that radiation use declined with age, decreasing from 80% in women 70–75 years of age to 41% for women over 80 years of age, compared with the overall 6% decline.

Our data also indicate that the use of radiation decreased as the Suemoto index increased, suggesting that mortality was considered in the decision-making process. In contrast, Soulos et al. used a SEER dataset to evaluate the use of RT among Medicare beneficiaries 3 years before and after publication of the CALGB 9343 study, and found a minimal and equivalent (between 3% and 4%) decrease in radiation between those with life expectancies > 10 years and those with life expectancies < 5 years at the time of treatment.[17] When the use of RT was evaluated by 5-year age groups in our study, the Suemoto index, used as a surrogate for life expectancy, was not associated with the use of adjuvant radiation. Thus, age alone may have been a larger consideration than predicted mortality.

It is possible that the nearly 50% rate of omission of radiation seen in our study does not reflect the broader community practice of breast surgeons. Shumway et al. surveyed over 800 radiation oncologists and surgeons in 2015–2016. Despite the study time frame being even more recent than our study period, 40% of surgeons and 20% of radiation oncologists still responded that omission of radiation in this elderly population was not reasonable. Similarly, a significant proportion of respondents incorrectly identified the use of radiation in this group as improving patient survival, and overestimated the risk of local recurrence associated with radiation omission.[18]

Although radiation does not improve survival in this patient population, it does improve local control, and this risk reduction may be important to some women. In our study, recurrence was low, although, as expected, RFS was better in patients who received adjuvant radiation compared with those who did not (98% vs. 92%), but without a statistically significant difference in 5-year OS between groups. However, for some women, avoidance of local recurrence may have a significant impact on their quality of life, even though it may not improve their OS. Radiation is well tolerated, with minimal toxicity and good cosmesis in older women,[19] and hypofractionated treatment minimizes inconvenience by significantly decreasing the duration of treatment. A 2014 publication comparing the cost effectiveness of no radiation, external-beam RT (EBRT), and intensity-modulated RT (IMRT) in women eligible for the

CALGB 9343 study found that while EBRT was cost effective for older women with favorable breast cancer, the cost effectiveness decreased with increasing age and with a decreased expected 10-year survival, as well as with the use of IMRT or brachytherapy.[20] Thus, for women with a high likelihood of surviving 10 years, prevention of a local recurrence with adjuvant radiation may improve quality of life in a cost-effective manner. Despite this rationale, in our study on multivariable analysis, aside from tumor size, no factors known to increase risk of local recurrence, such as the presence of a poorly differentiated tumor or lymphovascular invasion, were associated with receipt of radiation.

Our data are limited in the ability to determine all of the factors used in decision making in this population due to their retrospective nature. Additionally, and not inconsequentially, we were not able to assess patient preference for the use of radiation and how this may have impacted its use.

CONCLUSION

It is clear that while omission of radiation in women $\geq$ 70 years of age with small, ER+ tumors has no impact on OS, the use of radiation in this population remains high, even at an academic center. Aside from age and tumor size, no consistent features, including those known to influence local recurrence, were associated with the use of adjuvant radiation. Additionally, within age groups, a patient's 10-year risk of mortality was not associated with the use of adjuvant radiation.

In this patient population, risk factors for recurrence, the patient's risk of death from competing comorbidities, and, most importantly, patient preference regarding tolerance for a local recurrence and quality of life related to RT, must be carefully balanced. The development of a model that incorporates risk factors for recurrence and risk of death from other causes to facilitate individualized care in this patient population is the next step in optimizing care.

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REFERENCES

1. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347(16):1227–32.
2. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, 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(16):1233–41.
3. Fisher B, Bryant J, Dignam JJ, Wickerham DL, Mamounas EP, Fisher ER, 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(20):4141–9.
4. Early Breast Cancer Trialists' Collaborative Group, Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378(9804):1707–16.
5. Hughes KS, Schnaper LA, Berry D, Cirrincione C, McCormick B, Shank B, 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(10):971–7.
6. Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol*. 2013;31(19):2382–7.
7. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM, on behalf of the PRIME II Investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol*. 2015;16(3):266–73.
8. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. Breast cancer, Version 4.2017, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw*. 2018;16(3):310–20.
9. Levinson W, Born K, Wolfson D. Choosing wisely campaigns: a work in progress. *JAMA*. 2018;319(19):1975–6.
10. Palta M, Palta P, Bhavsar NA, Horton JK, Blitzblau RC. The use of adjuvant radiotherapy in elderly patients with early-stage breast cancer: changes in practice patterns after publication of Cancer and Leukemia Group B 9343. *Cancer*. 2015;121(2):188–93.
11. McCormick B, Ottesen RA, Hughes ME, Javid SH, Khan SA, Mortimer J, Niland JC, et al. Impact of guideline changes on use or omission of radiation in the elderly with early breast cancer: practice patterns at National Comprehensive Cancer Network institutions. *J Am Coll Surg*. 2014;219(4):796–802.
12. Suemoto CK, Ueda P, Beltran-Sanchez H, Lebrao ML, Duarte YA, Wong R, et al. Development and validation of a 10-year mortality prediction model: meta-analysis of individual participant data from five cohorts of older adults in developed and developing countries. *J Gerontol A Biol Sci Med Sci*. 2017;72(3):410–6.
13. Herskovic AC, Wu X, Christos PJ, Nagar H. Omission of adjuvant radiotherapy in the elderly breast cancer patient: Missed opportunity? *Clin Breast Cancer*. 2018;18(5):418–431.
14. Chu QD, Zhou M, Peddi P, Medeiros KL, Wu XC. Outcomes in real-world practice are different than cooperative trial for elderly patients with early breast cancer treated with adjuvant radiation therapy. *Surgery*. 2018;163(6):1213–9.
15. Chesney TR, Yin JX, Rajaee N, Tricco AC, Fyles AW, Acuna SA, et al. Tamoxifen with radiotherapy compared with Tamoxifen alone in elderly women with early-stage breast cancer treated with breast conserving surgery: a systematic review and meta-analysis. *Radiother Oncol*. 2017;123(1):1–9.
16. Fyles AW, McCready DR, Manchul LA, Trudeau ME, Merante P, Pintilie M, Weir LM, 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(10):963–70.
17. Soulos PR, Yu JB, Roberts KB, Raldow AC, Herrin J, Long JB, et al. Assessing the impact of a cooperative group trial on breast cancer care in the medicare population. *J Clin Oncol*. 2012;30(14):1601–7.
18. Shumway DA, Griffith KA, Sabel MS, Jones RD, Forstner JM, Bott-Kothari TL, et al. Surgeon and radiation oncologist views on omission of adjuvant radiotherapy for older women with early-stage breast cancer. *Ann Surg Oncol*. 2017;24(12):3518–26.
19. Cao KI, Salviat F, Laki F, Falcou MC, Carton M, Poortmans P, et al. Outcomes of postoperative radiation therapy for breast cancer in older women according to age and comorbidity status: an observational retrospective study in 752 patients. *J Geriatr Oncol*. 2018;9(6):600–605.
20. Sen S, Wang SY, Soulos PR, Frick KD, Long JB, Roberts KB, et al. Examining the cost-effectiveness of radiation therapy among older women with favorable-risk breast cancer. *J Natl Cancer Inst*. 2014;106(3):dju008.