VOLUME 31 · NUMBER 19 · JULY 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Kevin S. Hughes, Lauren A. Schnaper, Jennifer R. Bellon, Constance T. Cirrincione, Donald A. Berry, Beryl McCormick, Hyman B. Muss, Barbara L. Smith, Clifford A. Hudis, Eric P. Winer, and William C. Wood

See accompanying editorial on page 2367 and article on page 2377

Kevin S. Hughes and Barbara L. Smith, Massachusetts General Hospital; Jennifer R. Bellon and Eric P. Winer, Dana-Farber Cancer Institute, Boston, MA; Lauren A. Schnaper, Greater Baltimore Medical Center, Baltimore, MD; Constance T. Cirrincione, Alliance/Cancer and Leukemia Group B Statistics and Data Center, Duke University, Durham; Hyman B. Muss, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC; Donald A. Berry, University of Texas MD Anderson Cancer Center, Houston, TX; Beryl McCormick and Clifford A. Hudis, Memorial Sloan-Kettering Cancer Center, New York, NY; and William C. Wood, Emory University School of Medicine, Atlanta, GA.

Published online ahead of print at www.jco.org on May 20, 2013.

Written on behalf of the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and Eastern Cooperative Oncology Group.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Kevin S. Hughes, MD, FACS, Surgical Director, Breast Screening, Co-Director, Avon Comprehensive Breast Evaluation Center, Massachusetts General Hospital, Associate Professor of Surgery, Harvard Medical School, 55 Fruit St, Yawkey 7, Boston, MA 02114; e-mail: kshughes@partners.org.

0732-183X/13/3119w-2382w/$20.00

DOI: 10.1200/JCO.2012.45.2615

ABSTRACT

Purpose
To determine whether there is a benefit to adjuvant radiation therapy after breast-conserving surgery and tamoxifen in women age ≥ 70 years with early-stage breast cancer.

Patients and Methods
Between July 1994 and February 1999, 636 women (age ≥ 70 years) who had clinical stage I (T1N0M0 according to TNM classification) estrogen receptor (ER) –positive breast carcinoma treated by lumpectomy were randomly assigned to receive tamoxifen plus radiation therapy (TamRT; 317 women) or tamoxifen alone (Tam; 319 women). Primary end points were time to local or regional recurrence, frequency of mastectomy, breast cancer–specific survival, time to distant metastasis, and overall survival (OS).

Results
Median follow-up for treated patients is now 12.6 years. At 10 years, 98% of patients receiving TamRT (95% CI, 96% to 99%) compared with 90% of those receiving Tam (95% CI, 85% to 93%) were free from local and regional recurrences. There were no significant differences in time to mastectomy, time to distant metastasis, breast cancer–specific survival, or OS between the two groups. Ten-year OS was 67% (95% CI, 62% to 72%) and 66% (95% CI, 61% to 71%) in the TamRT and Tam groups, respectively.

Conclusion
With long-term follow-up, the previously observed small improvement in locoregional recurrence with the addition of radiation therapy remains. However, this does not translate into an advantage in OS, distant disease-free survival, or breast preservation. Depending on the value placed on local recurrence, Tam remains a reasonable option for women age ≥ 70 years with ER-positive early-stage breast cancer.

J Clin Oncol 31:2382-2387. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Radiation therapy (RT) after breast-conserving surgery decreases the risk of ipsilateral breast recurrence (IBTR). Several studies have suggested that there exists a favorable subgroup of patients in whom irradiation may not provide meaningful overall benefit, including but not limited to older women with smaller estrogen receptor (ER) –positive cancers treated with antihormonal therapy.[1-5] To test this hypothesis, the Cancer and Leukemia Group B (CALGB) initiated CALGB 9343, a randomized trial comparing the efficacy of tamoxifen alone (Tam) with tamoxifen plus RT (TamRT) in older women with ER-positive, clinical stage I breast cancer.

When reported in 2004 (median follow-up, 5 years),[6] the 5-year incidence of IBTR or regional nodal recurrence was 4% for patients receiving Tam and 1% for those receiving TamRT. There was no difference in survival, time to distant metastasis, or ultimate breast-preservation rate. Examining Medicare data through 2007, Soulis et al[7] found that our report had little impact, with the use of irradiation only slightly diminishing in this population. Because it was possible that with longer-term follow-up our results might not persist, we performed this long-term analysis to address these concerns.

PATIENTS AND METHODS

The methods of this study have been previously described.[6] CALGB 9343 was designed in cooperation with the Eastern Cooperative Oncology Group (ECOG) and

Radiation Therapy Oncology Group (RTOG). Local institutional review boards reviewed and approved the study in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients. An independent data and safety monitoring committee provided oversight. The CALGB Statistical Center managed data collection, and data quality was ensured by the study chairperson and statistical center review. CALGB statisticians performed the statistical analyses. The CALGB quality-assurance program has been previously described.[6]

Patient Selection

Women age ≥ 70 years with clinical stage I, ER-positive breast cancer and no history of cancer other than in situ cervical or nonmelanoma skin cancer within 5 years were eligible. Initial eligibility criteria included breast cancers up to 4 cm regardless of estrogen receptor status, but this was reduced in August 1996 to ≤ 2 cm (T1) with ER-positive or indeterminate receptor status. Patients were required to have clinically negative axillae.

Treatment

At entry, patients were randomly assigned (1:1 ratio) to receive Tam or TamRT.[6] Random assignment was stratified by age (< 75 *v* ≥ 75 years) and axillary dissection (yes *v* no). Patients were observed every 4 months for 5 years and yearly thereafter. This study did not rigorously capture tamoxifen discontinuation.

Local therapy. All women underwent lumpectomy with a clear margin (absence of tumor at the inked margin). Axillary node dissection was allowed but not encouraged. RT included tangential fields to the entire breast followed by an electron boost to the lumpectomy site.[6]

Tamoxifen. All women received 20 mg of tamoxifen per day for 5 years, initiated either during or after irradiation. Adjuvant hormonal treatment beyond 5 years was discretionary.

Study End Points

The primary study end points were time to locoregional recurrence, frequency of mastectomy for recurrence, breast cancer–specific survival, time to distant metastasis, and overall survival (OS). IBTR was defined as any cancer in the ipsilateral breast. Regional recurrence was defined as any recurrence in the ipsilateral supraclavicular, infraclavicular, or axillary nodes. Secondary end points were cosmetic results, as judged by physician and patient, and adverse effects such as breast pain and skin changes.

Actuarial Survival

The expected proportion of women in this study who would be alive at each year after random assignment was found assuming the women were randomly sampled from women of the same age in the general population. We used the 2001 period life table of the US Social Security Administration (approximate middle of follow-up for this study). We compared actual survival proportion and its confidence limits over time after random assignment of women in the study with their actuarial survival distribution.

Statistical Analysis

This study was designed with 90% power to detect a (one-sided) difference in 3-year locoregional recurrence between Tam at 16% versus TamRT at 9%. The target sample size was 572 patients; however, we overaccrued the study to 647 to compensate for the smaller than expected number of observed events.

The primary comparison of treatment arm on time-to-event end points used proportional hazards modeling adjusted for tumor size, patient age, and axillary dissection. Hazard ratios (HRs), constructed as TamRT to Tam, and their 95% CIs were taken from these multivariate models. Distributions of time-to-event variables were estimated according to the Kaplan-Meier method,[8] and distributions were compared between treatment groups by means of the log-rank test.[9] All *P* values are two sided and unadjusted for multiplicity. In terms of survival, the study was not powered to prove noninferiority.

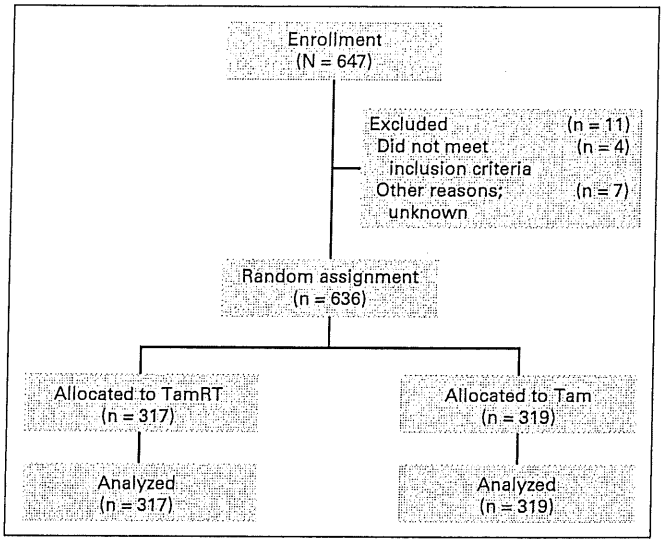

Fig 1. CONSORT diagram. Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

RESULTS

The study was initiated by the CALGB (July 1994) and by the RTOG and ECOG (December 1996). Enrollment ended in February 1999 with 647 women: CALGB, 307; ECOG, 112; and RTOG, 228 (Fig 1). Eleven patients (2%) never began protocol treatment. Statistical analyses used a modified intent-to-treat approach that included all 636 patients who began protocol treatment: 317 with TamRT and 319 with Tam. Before the eligibility change, 10 patients with ER-negative tumors and 13 patients with tumors > 2 cm were entered. Baseline characteristics of the women were similar in the two groups (Appendix Table A1, online only).

As of January 2011, median follow-up was 12.6 years (maximum, 16.5 years). Of the 636 treated patients, 335 (53%) survived at least 10 years, 227 of whom remain in active follow-up. Because the observed treatment effect was similar when assessed by both log-rank and multivariate methods, we quote the *P* values from only the log-rank test.

Time to Locoregional Recurrence

As compared with the Tam group, the TamRT group experienced a significantly longer time to locoregional recurrence (observed HR, 0.18; 95% CI, 0.07 to 0.42; $P < .001$; Fig 2). At 10 years, 90% of patients in the Tam group (95% CI, 85% to 93%) compared with 98% in the TamRT group (95% CI, 96% to 99%) were free from locoregional recurrence. Thirty-two women in the Tam group experienced locoregional recurrence; of these, 20 had only IBTR; six, IBTR with distant metastasis; five, only axillary recurrence; and one, both IBTR and axillary recurrence. Six women in the TamRT group experienced locoregional recurrence; all six were IBTRs (Table 1). At 10 years, 91% in the Tam group (95% CI, 87% to 94%) compared with 98% in the TamRT group (95% CI, 96% to 99%) were free from local (IBTR) recurrence.

There were no axillary recurrences among the 244 women who underwent initial axillary dissection. Among those who did not undergo axillary dissection, there were no axillary recurrences in the TamRT group; there were six of 200 in the Tam group.

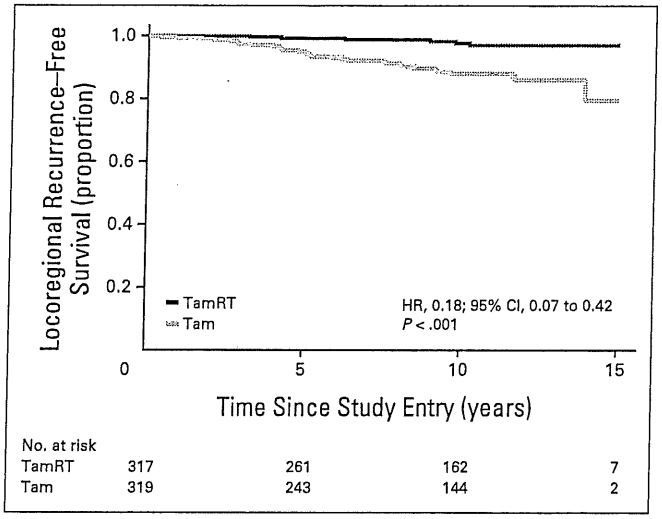

Fig 2. Time to local or regional recurrence. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

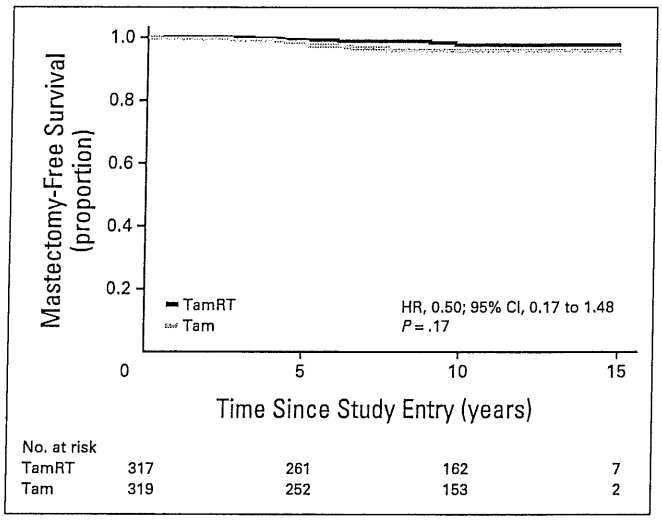

Fig 3. Time to subsequent mastectomy. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

Treatment of IBTR

Six patients receiving TamRT and 27 receiving Tam had in-breast recurrences (IBTRs). Of these, four (TamRT) and 10 (Tam) underwent mastectomy. One patient in the TamRT arm underwent lumpectomy without RT; 13 in the Tam arm underwent lumpectomy (four without RT, eight with RT, and one unknown RT).

Time to Mastectomy

Time to mastectomy did not differ significantly between the two treatment groups (observed HR, 0.50; 95% CI, 0.17 to 1.48; $P = .17$; Fig 3). The 10-year probability of not undergoing mastectomy was 98% (95% CI, 96% to 99%) in the TamRT group and 96% (95% CI, 93% to 98%) in the Tam group.

Time to Distant Metastasis

Time to distant metastasis did not differ significantly between the two treatment groups ($P = .50$; Fig 4); distant relapse occurred in 21 patients in the TamRT group (13 have died as a result of breast cancer) and 16 in the Tam group (eight have died as a result of breast cancer). The 10-year probability of freedom from distant metastasis was 95% (95% CI, 92% to 97%) in the TamRT group and 95% (95% CI, 91% to 97%) in the Tam group (observed HR, 1.20; 95% CI, 0.63 to 2.32).

Survival

Of the 636 women in the trial, there were 334 deaths: 166 in the TamRT arm and 168 in the Tam arm (HR, 0.95; 95% CI, 0.77 to 1.18). The respective 10-year estimates of OS were 67% (95% CI, 62% to 72%) and 66% (95% CI, 61% to 71%; Fig 5). Only 21 of the deaths (6.3%) resulted from breast cancer: 13 in the TamRT arm and eight in the Tam arm (HR, 1.55; 95% CI, 0.64 to 3.74). The respective 10-year breast cancer–specific survival estimates (Appendix Fig A1, online only) were 97% (95% CI, 94% to 99%) and 98% (95% CI, 95% to 99%). Figure 6 shows survival proportion over time for women in this study (both groups combined) in comparison with the expected survival proportion of age-matched women in the general population.

Table 1. Clinical Outcome: Recurrence and Death

Treated Patients	TamRT Arm	Tam Arm	Total
Total	317	319	636
Recurrence	23	42	65
Local or regional ± distant	6	32	38
IBTR alone	2	20	22
Axilla alone	0	5	5
IBTR with axilla	0	1	1
IBTR with distant	4	6	10
Distant alone	17	10	27
Death			
All cause	166	168	334
Breast cancer specific	13	8	21

Abbreviations: IBTR, ipsilateral breast recurrence; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

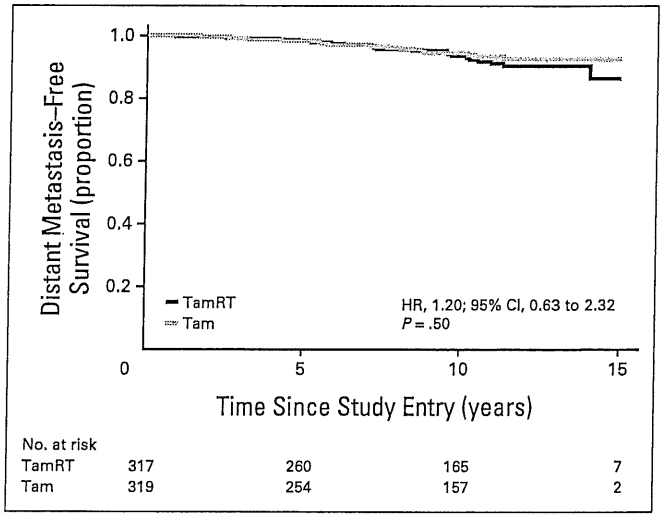

Fig 4. Time to distant metastasis. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

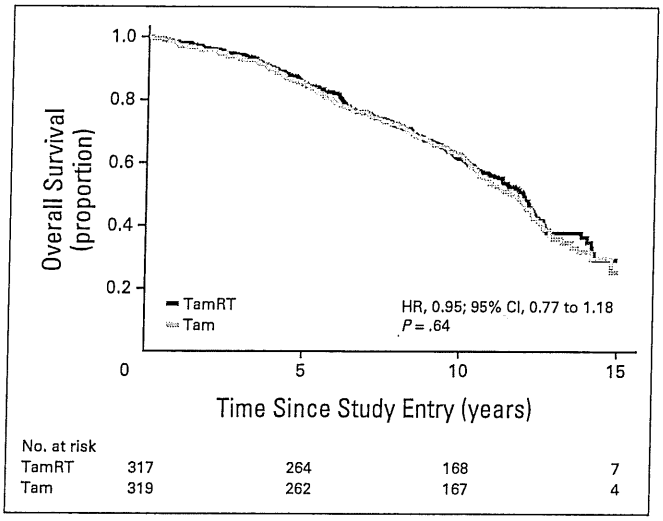

Fig 5. Overall survival. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

Noninferiority

The study lacks the power to prove that the trend toward greater survival (HR, 0.95) and time to mastectomy (HR, 0.50) in the TamRT group or the trend toward greater breast cancer–specific survival (HR, 1.55) and freedom from distant metastasis (HR, 1.20) in the Tam arm would not continue.

DISCUSSION

At a median follow-up of 12.6 years, we demonstrate that at 10 years, the incidence of locoregoreginal recurrence is 8% lower, and the incidence of IBTR is 7% lower, with TamRT versus Tam alone. This difference is statistically significant. The addition of RT seems to provide no benefit in terms of OS, distant disease-free survival, or ultimate breast preservation, with the proviso that the study lacked the power to definitively show noninferiority of either arm. Importantly, the study also shows that the impact of breast cancer in this select group of older women is much smaller than that of comorbid conditions. Of the 636 women in this study, only 21 (3%) have died as a result of breast cancer, whereas 313 (49%) have died as a result of other causes (only 6% of deaths attributed to breast cancer).

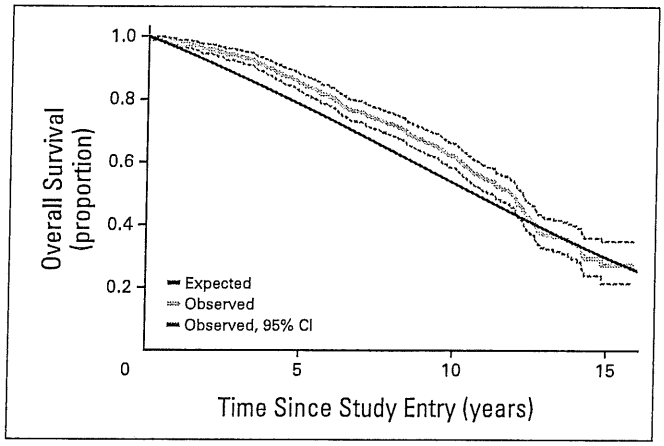

Fig 6. Observed versus expected survival.

As breast conservation became an accepted approach in the 1980s, it was thought that there were subgroups of women in whom RT might be safely eliminated. Several randomized trials were initiated that compared the efficacy of Tam versus TamRT after lumpectomy (Appendix Table A2, online only). All were based on the premise that women at low risk of recurrence might benefit from less treatment. Trials used varying combinations of postulated low-risk factors, such as older age, smaller tumors, and tumors with favorable prognostic factors. Although all of the trials examined the question of eliminating RT, CALGB 9343 differed from other trials in the factors chosen for eligibility. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B21 trial[1] was based on tumor size of ≤ 1 cm, included younger women, and had three arms: Tam, TamRT, and RT placebo. The Austrian Breast and Colorectal Cancer Study Group trial[4] had a mean age of 66 years, tumor size < 3 cm, and hormone treatment with either tamoxifen or anastrazole. The German Breast Cancer Group trial (GBCG-V)[5] allowed women as young as age 45 years and used a 2×2 factorial design (RT or no RT; Tam or no Tam). The British Association of Surgical Oncology (BASO) BASO II trial[2] followed a similar 2×2 factorial design. Tinterri et al[10] randomly assigned women between the ages of 55 and 75 years to either RT and no RT but allowed systemic therapy as dictated by tumor characteristics. Despite the differences in design, no study showed significant differences in distant disease-free survival or OS, although all showed some decrease in IBTR with RT. The differences in terms of eligibility criteria likely account for the differences seen in the effect of RT on breast recurrence.

CALGB 9343 was originally conceived based on several observations. First, adjuvant RT after breast-conserving surgery does not change survival. The Early Breast Cancer Trialists' Collaborative Group 2005 meta-analysis[11] reported a significant reduction in mortality at 15 years with RT, but it is clear that this only applied if the difference in IBTR was $> 10\%$. Most trials reported here revealed a difference in IBTR of $< 10\%$. The data continue to support no survival advantage with the addition of adjuvant RT in the cohorts represented by these trials.

Second, older women have fewer local recurrences. The Milan III trial[12] suggested that with quadrantectomy and axillary dissection alone, the rate of IBTR decreased with advancing age. Women age < 45 years had a 17.5% rate of IBTR, whereas those age > 55 years had a 3.8% rate of IBTR. The trials listed in Appendix Table A2 (online only) reinforce this finding, demonstrating a trend toward higher IBTR in younger women with or without RT.

Third, adjuvant Tam after breast conservation decreases the risk of in-breast recurrence.[13] Older women tend to have estrogen-sensitive tumors,[14] and tamoxifen efficacy increases directly with levels of estrogen receptor expression.[15] Tumor estrogen and progesterone receptor levels increase over time with maximum expression in women age > 75 years.[16] Moreover, when compared with Tam, aromatase inhibitors (AIs) seem to show an even further decrease in risk of IBTR.[17] In a meta-analysis of randomized trials comparing 5 years of either adjuvant Tam or an AI, patients receiving an AI had an HR of 0.70 for isolated local recurrence as a first event (two-sided $P = .03$).

Fourth, local recurrence after breast-conserving treatment without irradiation can be salvaged by repeat lumpectomy or lumpectomy

with RT. Preservation of the breast, even after IBTR, has been demonstrated by Liligren et al,[18] Clark et al,[19] and Veronesi et al.[12] In our study, there was no significant difference in ultimate rate of breast preservation.

We note that the definition of negative margins has changed since this study began. CALGB 9343 accepted the NSABP standard of no ink on tumor, essentially a one-cell minimum margin. Today, the trend is toward greater negative margins, usually 1 to 2 mm,[20,21] and the low rate of IBTR without RT in this study might further decrease with wider excision, suggesting that any benefit of RT over antiestrogen treatment alone in local recurrence may be of even less significance today.

In our study, treatment of the axilla was left to the discretion of the physician. Among women who did not have an axillary dissection upfront, none in the TamRT arm experienced recurrence in the axilla; however, six (3%) in the Tam arm did. In the absence of RT or sentinel node biopsy, we might expect a 3% increase in local control compared with RT or sentinel node biopsy. If the results of a sentinel node biopsy are not likely to change the choice of systemic treatment, it is questionable whether this 3% decrement warrants the use of sentinel node biopsy in this population.

Fifth, shorter life expectancy in older women leaves less time for local recurrence. We anticipated that many women would die as a result of competing causes in a relatively short period of time and thus not live long enough to be at risk for IBTR. This was not correct, because the median survival was 12 years, and yet the rate of IBTR remained low. We would suggest that in this older population, comorbid conditions, not specific breast cancer treatments, dictate survival, and the biology of the tumor dictates the rate of IBTR, not the length of life.

Time to distant metastasis did not differ between the two treatment groups and continues to be low. The 10-year incidence of distant disease was only 5% in the Tam RT group and 5% with Tam alone.

The women in this study were significantly healthier and lived considerably longer than the general population of that set of ages. This suggests that the results of this study apply to healthy women in this age group, not just to those with comorbidities.

The durability of the results of this study is encouraging. When first presented, there was concern that with longer follow-up, the number of recurrences would increase. However, the number of events for both groups remains low. With median follow-up of 12.6 years, 334 of 636 women have died, but only 21 (6%) of these have died as a result of breast cancer. In comparison with our previous report of these results at median follow-up of 5 years,[6] as expected, the all-cause mortality proportion has increased, but it is still similar between the two arms. The 10-year incidence of breast cancer survival is low in both arms.

The toxicity of tamoxifen is not trivial, particularly in this elderly population. Well-known adverse effects include hot flashes, thrombotic events, and a small risk of endometrial cancer.[22] However, despite the possibility that all patients were not able to complete the prescribed course of treatment, local control, distant disease-free survival, and cancer-specific survival remained excellent in this population with generally favorable disease characteristics.

Despite the observed similarity in OS and absolute risk reduction by breast irradiation in locoregional recurrence of only 7%, this study has not had a notable impact on clinical practice. The recent article by Soulos et al[7] found that RT use decreased < 5% after publication and dissemination of the data. The decision to use RT may depend more on concerns about our initial short-term 5-year follow-up, patient perception of substandard treatment, choosing the length of time for RT versus tamoxifen, financial considerations, and physician equipoise. The editorial by Giordano[23] accompanying that article suggested that given the same level of significance, physicians are more likely to adopt a change in practice that adds or enhances a treatment, rather than a change in which a treatment is withdrawn.

CALGB 9343 was conceived based on the hypothesis that there was a subset of patients in NSABP B06 who did not benefit from breast irradiation after lumpectomy. We observed the indolent behavior of breast cancer in older women in everyday clinical practice and used that as the basis for our study design. Our goal was to offer this cohort of women another treatment option that might decrease morbidity, allow for adaption to social issues, and not complicate other medical problems. Our study offers evidence that such women should have the option of breast-conserving therapy even without RT.

Long-term follow-up of CALGB 9343 confirms and extends the earlier report that in women age ≥ 70 years with clinical stage I, ER-positive breast cancer treated with lumpectomy followed by tamoxifen, irradiation adds no significant benefit in terms of survival, time to distant metastasis, or ultimate breast preservation, even though it provides a small decrease in IBTR.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Kevin S. Hughes, Lauren A. Schnaper, Constance T. Cirrincione, Donald A. Berry, Hyman B. Muss, William C. Wood
Administrative support: Kevin S. Hughes, Constance T. Cirrincione, Beryl McCormick, Hyman B. Muss, Clifford A. Hudis, Eric P. Winer, William C. Wood
Provision of study materials or patients: Kevin S. Hughes, Beryl McCormick, Hyman B. Muss, Barbara L. Smith, Clifford A. Hudis, Eric P. Winer, William C. Wood
Collection and assembly of data: Kevin S. Hughes, Constance T. Cirrincione, Donald A. Berry, Beryl McCormick
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. 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 20:4141-4149, 2002
2. Blamey RW, Chetty U, Bates T, et al: Radiotherapy and/or tamoxifen after conserving surgery for breast cancers of excellent prognosis: BASO II trial. Eur J Cancer 6:55, 2008 (suppl)
3. Fyles AW, McCready DR, Manchul LA, et al: Tamoxifen with or without breast irradiation in women 50 years or older with early breast cancer. N Engl J Med 351:963-970, 2004
4. Pötter R, Gnant M, Kwasny W, et al: Lumpectomy plus tamoxifen or anastrozole with or without whole breast irradiation in women with favorable early breast cancer. Int J Radiat Oncol Biol Phys 68:334-340, 2007

5. Winzer KJ, Sauerbrei W, Braun M, et al: Radiation therapy and tamoxifen after breast-conserving surgery: Updated results of a 2×2 randomised clinical trial in patients with low risk of recurrence. Eur J Cancer 46:95-101, 2010

6. 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 351:971-977, 2004

7. Soulos PR, Yu JB, Roberts KB, et al: Assessing the impact of a cooperative group trial on breast cancer care in the Medicare population. J Clin Oncol 30:1601-1607, 2012

8. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

9. Peto R, Pike MC, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II. Analysis and examples. Br J Cancer 35:1-39, 1977

10. Tinterri C, Gatzemeier, Zanini V, et al: Conservative surgery with and without radiotherapy in elderly patients with early-stage breast cancer: A prospective randomized multicentre trial. Breast 18: 373-377, 2009

11. 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 366:2087-2106, 2005

12. Veronesi U, Luini A, Del Vecchio M, et al: Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. N Engl J Med 328:1587-1591, 1993

13. Fisher B, Constantino J, Redmond C, et al: Tamoxifen treatment for breast cancer: A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N Engl J Med 320:479-484, 1989

14. Wyld L, Reed MW: The need for targeted research into breast cancer in the elderly. Br J Surg 90:388-389, 2003

15. Tamoxifen for early breast cancer: An overview of the randomised trials—Early Breast Cancer Trialists' Collaborative Group. Lancet 351:1451-1467, 1998

16. Gennari R, Curigliano G, Rotmenz N, et al: Breast carcinoma in elderly women: Features of disease presentation, choice of local and systemic treatments compared with younger postmenopausal patients. Cancer 101:1302-1310, 2004

17. Dowsett M, Cuzick J, Ingle J, et al: Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol 28:509-518, 2010

18. Liljegren G, Holmberg L, Adami HO, et al: Sector resection with or without postoperative radiotherapy for stage I breast cancer: Five-year results of a randomized trial—Uppsala-Orebro Breast Cancer Study Group. J Natl Cancer Inst 86:717-722, 1994

19. Clark RM, McCulloch PB, Levine MN, et al: Randomized clinical trials to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. J Natl Cancer Inst 84:683-689, 1992

20. Azu M, Abrahamse P, Katz SJ, et al: What is an adequate margin for breast-conserving surgery? Surgeon attitudes and correlates. Ann Surg Oncol 17:558-563, 2010

21. Kaufmann M, Morrow M, Von Minckwitz G, et al: Locoregional treatment of primary breast cancer: Consensus recommendations from an international expert panel. Cancer 116:184-191, 2010

22. Amir E, Seruga B, Niraula S, et al: Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: A systematic review and meta-analysis. J Natl Cancer Inst 103:1299-1309, 2011

23. Giordano SH: Radiotherapy in older women with low-risk breast cancer: Why did practice not change? J Clin Oncol 30:1577-1578, 2012

Appendix

Table A1. Patient Demographic and Clinical Characteristics

Characteristic	TamRT Arm		Tam Arm		Total	
	No.	%	No.	%	No.	%
Treated patients	317	100	319	100	636	100
Stratification						
ER status						
Positive	313	99	313	98	626	98
Negative	4	1	6	2	10	2
Tumor size, cm						
≤ 2	310	98	313	98	623	98
> 2	7	2	6	2	13	2
Age at enrollment, years						
< 75	141	44	147	46	288	45
≥ 75	176	56	172	54	348	55
Demographics						
Race						
White	287	91	287	90	574	90
Hispanic	5	2	8	3	13	2
Black	23	7	22	7	45	7
Asian	0	0	2	1	2	< 1
Other	1	< 1	0	0	1	< 1
Unknown	1	< 1	0	0	1	< 1
Diagnostic axillary involvement						
Underwent axillary dissection	122	38	119	37	241	38

Abbreviation: ER, estrogen receptor; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

Table A2. Studies Examining the Role of Irradiation After Breast-Conserving Surgery

Study	No. of Patients	Follow-Up (years)	Age (years)	Tumor Size (cm)	Treatment	Local Recurrence	Statistical Significance
CALGB 9343	636	10.5	≥ 70	≤ 2.0	Tam	9	< .001*
					TamRT	2	
NSABP B21[1]	1,009	8	Any age	< 1	Tam	17	< .001
					TamRT	3	
					RT placebo	9	
Winzer et al[5]	361†	10	45-75	≤ 2	Surgery alone	34	< .001
					Surgery plus RT	10	
					Surgery + tamoxifen	8	
					Surgery + RT + tamoxifen	9	
Potter et al[4]	869	4.5	Postmenopausal (mean, 66)	≤ 3	Tam or AI	6	< .001
					Tam or AI + RT	2	
Fyles et al[3]	769	5.6	> 50	≤ 5	Tam	8	.001
					TamRT	1	
Tinterri et al[10]	749	5.0	55-75	< 2.5	Surgery alone	3	.07
					Surgery + RT	1	
Forrest et al‡	585	6	< 70	≤ 4	Tam§	25	NS
					TamRT	6	

Abbreviations: AI, aromatase inhibitor; CALGB, Cancer and Leukemia Group B; NS, not stated; NSABP, National Surgical Adjuvant Breast and Bowel Project; RT, radiation therapy; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

*Locoregional recurrence.

†347 analyzed.

‡Forrest et al: Lancet 348:708-713, 1996.

§Or cyclophosphamide, methotrexate, and fluorouracil based on estrogen receptor status.

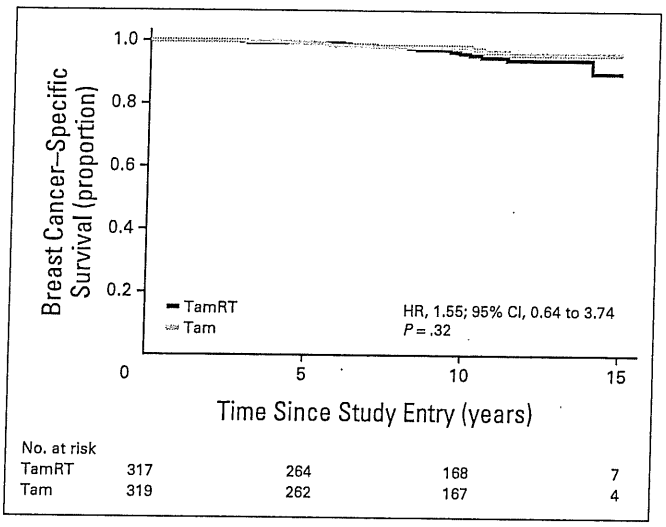

Fig A1. Breast cancer–specific survival. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

VOLUME 31 · NUMBER 19 · JULY 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ONCOLOGY GRAND ROUNDS

Should a Woman Age 70 to 80 Years Receive Radiation After Breast-Conserving Surgery?

Jaroslaw T. Hepel, *Rhode Island Hospital, Alpert Medical School of Brown University, Providence, RI*
David E. Wazer, *Tufts Medical Center, Tufts University School of Medicine, Boston, MA; and Rhode Island Hospital, Alpert Medical School of Brown University, Providence, RI*

See accompanying article on page 2382

The Oncology Grand Rounds series is designed to place original reports published in the Journal *into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors' suggested management approaches. The goal of this series is to help readers better understand how to apply the results of key studies, including those published in* Journal of Clinical Oncology, *to patients seen in their own clinical practice.*

Case 1: A 72-year-old woman presents with a palpable mass detected during yearly physical examination by her primary care physician. She has controlled hypertension and remains active, playing tennis three times a week. Physical examination reveals a 1.5 cm mass in the upper outer quadrant of the left breast with no palpable axillary lymphadenopathy. Diagnostic imaging reveals a suspicious mass, and core biopsy confirms invasive ductal carcinoma (IDC) that is estrogen receptor moderately positive (60%), progesterone receptor negative and Her2-*neu* that is not overexpressed. She undergoes a wide local excision and sentinel node biopsy. Pathology reveals a 1.5 cm IDC that is high grade without lymphovascular invasion (LVI). The margins are negative with the closest laterally at 2 mm. One sentinel node is negative for metastasis.

Case 2: A 72-year-old woman presents with an abnormal screening mammogram that shows a small area of architectural distortion in the upper outer quadrant of the left breast (Fig 1). She is a former smoker with mild chronic obstructive pulmonary disease and has mild to moderately symptomatic osteoarthritis managed with a nonsteroidal anti-inflammatory agent. She remains active and independent. Physical examination reveals neither palpable breast mass nor axillary lymphadenopathy. Diagnostic ultrasound confirms a 1.8 cm mass, and core biopsy reveals IDC that is estrogen and progesterone receptor strongly positive (> 90%) and Her2-*neu* that is not overexpressed. She undergoes a wide local excision and sentinel node biopsy. Pathology reveals a 1.9 cm IDC that is low grade. The margins are widely negative at > 5 mm and there is no LVI. One sentinel node is negative for metastasis.

CHALLENGES IN DIAGNOSIS AND MANAGEMENT

Radiation therapy represents an integral part of breast-conserving therapy (BCT), as multiple trials have consistently shown increased rates of ipsilateral breast tumor recurrence (IBTR) in women undergoing breast-conserving surgery when radiation therapy is omitted. In addition to the effect on local tumor recurrence, radiotherapy after breast-conserving surgery reduces the risk of death, as demonstrated in the recent update of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, where radiotherapy was found to lower the risk of breast cancer death by one sixth.[1]

The local management of older patients with early stage breast cancer presents a special set of challenges. In an elderly patient, toxicity concerns may be more prominent than for a younger patient and, as such, often influence the assessment of the risks and benefits of any treatment course. Even so, clinicians must be mindful to avoid subtle or overt discrimination that can manifest by withholding treatment based solely on chronologic age. When making decisions about therapeutic options, it is appropriate to consider what is sometimes characterized as biologic age, which can be roughly described as an estimate of life expectancy assessed through an evaluation of competing risks for mortality from comorbid conditions. Clearly, if a patient with breast cancer is expected to receive no discernable benefit from local radiation therapy and to experience death from a cause unrelated to breast cancer, then it makes little sense to subject her to the financial cost and the risk of adverse effects associated with the treatment.

The biology of breast cancer varies considerably with age, and it is independent of other known tumor-related characteristics.[2] Increasing age has been shown to inversely correlate with the risk for local and

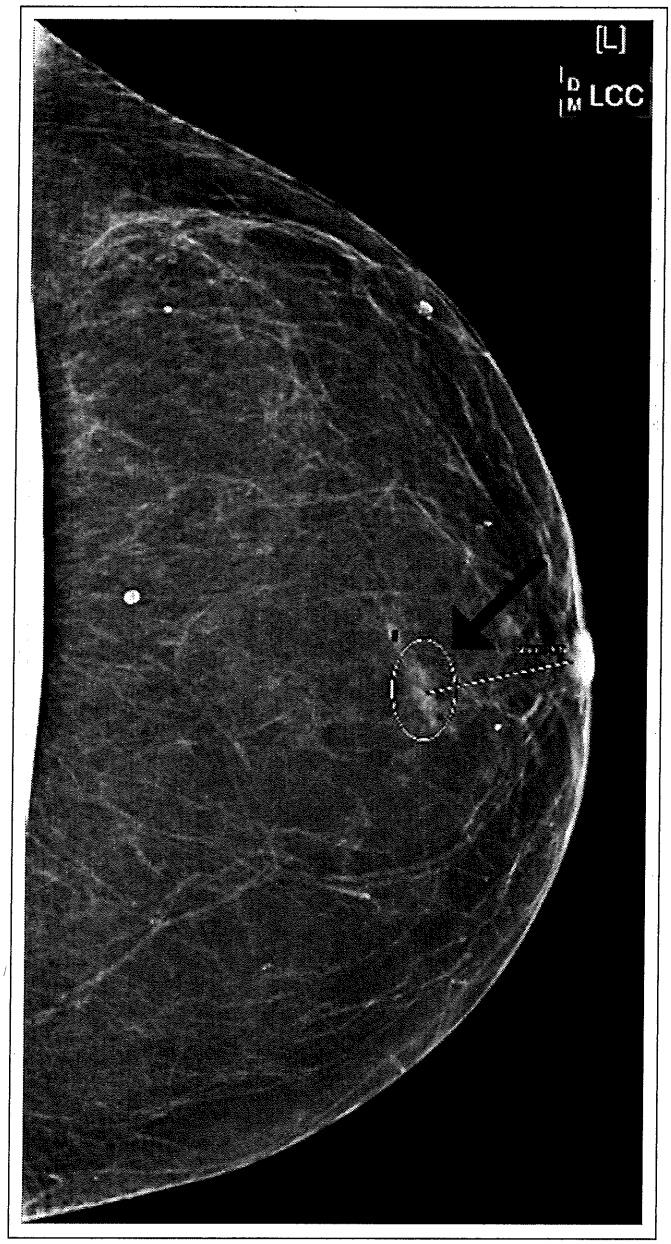

Fig 1. Left breast cranial-caudal view mammogram depicting a small area of architectural distortion suspicious for malignancy (black arrow). This abnormality was confirmed on spot compression views (not shown) and was new compared with previous mammography 1 year earlier. An ultrasound and biopsy were recommended.

distant disease recurrence and positively correlates with the likelihood of disease-specific survival.[1,3] Patients older than age 70 typically have low-grade, strongly estrogen receptor (ER) positive tumors that have an indolent natural history. However, this is not the case for all older patients, and, as such, factors that influence risk of local and systemic recurrence need to be considered for each individual.

Treatment options for early-stage breast cancer in elderly patients commonly considered after breast-conserving surgery include observation, endocrine therapy alone, endocrine therapy combined with radiation therapy, and radiation therapy alone. In contemporary clinical practice, endocrine therapy consists of either tamoxifen or an aromatase inhibitor administered daily for a period of at least 5 years. Adverse effects can include hot flashes, thrombotic events, and risk of endometrial cancer with tamoxifen, and hot flashes, arthralgias, and osteoporosis with aromatase inhibitors. Some of these adverse effects can be sufficiently bothersome to patients to result in as many as one third becoming noncompliant with the full prescribed course of endocrine therapy.[4,5] Radiation therapy typically consists of irradiation of the whole breast using a standard fractionated regimen delivered 5 days per week during a 6- to 7-week course. Adverse effects include fatigue and local skin irritation during treatment and long-term risks of rib fracture, pneumonitis, and cardiac injury. Although the adverse effect profile of endocrine therapy and radiation therapy are both favorable, relatively minor adverse effects that are well tolerated by a younger patient may be much more significant in an older patient. For example, aromatase inhibitor–related arthralgias or radiation-related fatigue has the potential of reducing a well-functioning older patient to one who is dependent in activities of daily living.

Recently, more convenient short-course radiation therapy options have become available. Hypofractionated whole-breast radiation therapy is delivered in approximately 3½ weeks and has been shown to be equally well tolerated and as effective as standard fractionated treatment.[6] In addition, older, low-risk breast cancer patients are classified by consensus statement of the American Society for Radiation Oncology as suitable for accelerated partial breast irradiation (APBI), which can be delivered during 1 week or less.[7]

The choice of radiation therapy approach is complex and dependent on both technique-specific considerations and patient preference. Hypofractionated whole-breast radiation therapy is appropriate for most older patients. Patients with a large body habitus or large breast size may not be ideal candidates for this approach, as the normal tissue effects resulting from radiation dose inhomogeneity are magnified by using hypofractionation and may result in a higher risk of acute and late toxicity.[8] APBI can be considered for patients at low risk for recurrence beyond the immediate tumor bed. According to the American Society for Radiation Oncology Consensus Statement, patients felt to be most appropriate for APBI are women older than 60 years with T1N0 tumors that are unifocal, ER positive, without LVI, and have $>$ 2 mm negative margins [7]. APBI may be a preferred option for patients with suboptimal lung or cardiac anatomy, where tangential whole breast irradiation would place these organs at excessive risk. APBI may also be a good option for patients with large breast size, as acute skin toxicity can be minimized as compared to whole breast irradiation. The APBI techniques that are associated with the most mature outcome data are interstitial multicatheter and intracavitary balloon catheter brachytherapy. As both techniques are invasive, they may not be acceptable to some patients. Novel minimally invasive or noninvasive APBI techniques are currently under investigation that may expand future options for APBI.

The patient's perspective as to the optimal course of therapy is often not limited to just the potential adverse effects, but may also extend to the convenience and lifestyle impact of the treatment course itself. As such, some will prefer the simplicity of an extended course of a daily oral medication to the disruption in daily routine that is associated with daily irradiation. Conversely, others will prefer a brief

Table 1. Absolute Risk Reduction at 10 Years in First Recurrence With Radiation Therapy on the Basis of Data From the EBCTCG Meta-Analysis

Women > 70 Years of Age With T1N0 and ER-Positive Tumors Treated With Lumpectomy		
Tumor Grade	Tamoxifen	No Tamoxifen
Low	5	11
Intermediate	9	19
High	20	38

NOTE. Table numbers represent absolute difference (%) in the rate of first recurrence between patients who received no radiation compared with those who received radiation. First recurrence includes locoregional or distant recurrence. Data from Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis.[1]
Abbreviation: ER, estrogen receptor.

period of radiation therapy over committing to consumption of a daily pill for 5 or more years.

SUMMARY OF THE RELEVANT LITERATURE

As noted, the EBCTCG meta-analysis of BCT showed a 50% reduction (35% *v* 19%) in recurrence with whole breast radiation therapy. Of note, however, a statistically significant increase in overall survival was limited to those patients for whom radiotherapy resulted in a recurrence reduction of 10% or greater.[1] In light of this threshold relationship between risk reduction in local failure and subsequent impact on breast cancer mortality, the clinical value of radiotherapy must be carefully considered in patients at low risk of recurrence.

There has been considerable effort expended during the past two decades to identify a cohort of patients at sufficiently low risk for local failure for whom radiation therapy may be safely omitted. The National Surgical Adjuvant Breast and Bowel Project B21 trial randomly assigned 1,009 women of all ages with small tumors (< 1.0 cm) that were ER positive to tamoxifen alone, radiation therapy alone, or tamoxifen and radiation therapy.[9] In a separate trial, Fyles et al[10] enrolled 769 women older than age 50 with T1or2N0 tumors that were ER positive and randomly assigned them to tamoxifen alone or tamoxifen and radiation therapy. In these putatively low-risk patient populations that spanned a broad spectrum of ages, both trials found a > 10% increase in local failure when radiation therapy was omitted.

Cancer and Leukemia Group B (CALGB) study 9343 incorporated older age as a prognostic variable in identifying a patient population suspected to be at particularly low risk for recurrence. Consistent with all prior randomized studies of BCT, the initial report of this trial after 5 years of follow-up showed a statistically significant lower rate of local failure with the addition of radiation therapy.[11] However, the 3% absolute reduction in the rate of local failure with radiotherapy was of dubious clinical significance, as there was no difference in the rates of subsequent mastectomy, distant metastases, or overall survival. On the basis of these findings, the treatment guidelines of the National Comprehensive Cancer Network were revised to state that radiotherapy may be reasonably omitted in women age 70 or older with ER-positive, stage I breast cancer who receive antiestrogen endocrine therapy.[12]

Remarkably, the initial results of CALGB 9343 and the subsequent revision in the National Comprehensive Cancer Network guidelines appeared to have minimal effect on the use of radiation therapy in older patients,[13] perhaps as a result of fear that with longer follow-up these findings might not persist. To address these concerns, an update of CALGB 9343 has been reported with a median follow-up duration of 12.6 years.[14] At 10 years, two thirds of the patients remained alive, and a statistically significant lower local failure rate continued to be associated with the administration of radiation therapy (2% *v* 10%). However, as with the earlier report, radiation therapy remained of minimal clinical value, as no difference was seen in the rate of subsequent mastectomy, breast cancer–specific survival, or overall survival. These results provide compelling confirmation of high-quality level I evidence that for this select patient population, the administration of tamoxifen and the omission of radiation therapy is a safe and reasonable treatment approach.

The CALGB 9343 trial, however, is deficient in some important respects that limit the application of its findings to all older women with T1N0 estrogen receptor–positive breast cancer. First, a subgroup analysis has not been performed that evaluates the impact of factors known to influence the risk of locoregional recurrence, including LVI and tumor grade. The EBCTCG meta-analysis showed that for patients with T1N0 estrogen receptor–positive tumors, high tumor

Table 2. Suggested Algorithm for Management of Women Older Than Age 70 Years With T1N0 and ER-Positive Invasive Breast Cancer

Life Expectancy	Risk Assessment	Considerations	Treatment
< 2 to 5 years	Severe comorbidity and minimal risks for local or systemic recurrence		Observation
> 5 years	Low risk for local or systemic recurrence	Relative side effects of treatment with radiation (CVD, COPD, or lung disease); tamoxifen (risk of thromboembolism); or aromatase inhibitor (arthritis/joint symptoms, osteoporosis)	Endocrine therapy alone or radiation therapy alone
	Dominant risk for local recurrence only	Risk factors: close or focally positive margins not amenable to re-excision	Radiation therapy alone
	Moderate to high risk for local and systemic recurrence	Risk factors: high grade, LVI, high recurrence score on multigene panel, or overexpression of HER2/*neu* (consider chemotherapy)	Endocrine therapy and radiation therapy

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, collagen vascular disease; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LVI, lymphovascular invasion.

grade is associated with markedly increased local failure risk, translating to a large absolute benefit for radiation therapy in patients treated with or without tamoxifen (Table 1).[1] A similar increase in risk might be encountered in the presence of other adverse pathologic findings, such as LVI. Therefore, it is impossible to definitively declare that there are no subpopulations within the cohort of older patients with T1N0 estrogen receptor–positive tumors who may be at substantial risk of local failure with tamoxifen alone and may show a clinically meaningful benefit with the addition of radiation therapy. Second, there is a lack of information related to other prognostic variables, including performance status, extent of medical comorbidities, and Her2-*neu* receptor status. Third, the design of CALGB 9343 was limited in scope as to the full range of possible treatment options that might be considered in these patients, in that it did not address the use of observation or radiation therapy alone. Most of the patients enrolled in CALGB 9343 were at low risk of both local and systemic recurrence. Therefore, the benefit of tamoxifen was likely predominantly limited to reduction of recurrence in the breast. The more relevant and practical clinical question faced in the management of the low-risk older patient with multiple comorbidities, limited life expectancy, and narrow tolerance to treatment adverse effects may not be tamoxifen versus tamoxifen plus radiation therapy, but tamoxifen alone versus radiation therapy alone versus observation only after local excision. Unfortunately, we lack prospective evaluation of the relative recurrence risk, compliance rate, toxicity, and quality of life assessment associated with the full spectrum of management approaches that are often considered in older patients.

SUGGESTED APPROACHES TO MANAGEMENT

Table 2 outlines a suggested approach to the local management of patients older than age 70 with estrogen receptor–positive stage I breast cancer. The dominant considerations are life expectancy and comorbid conditions. A thorough evaluation of medical history as well as performance status and overall function are critical for making this assessment. At the extreme, patients with severe medical comorbidity, a short life expectancy, and low-risk breast cancer are unlikely to experience local or systemic benefit from either endocrine therapy or radiation therapy. After wide excision of the local tumor, observation alone may be a reasonable option. For severely debilitated patients who are poor operative risks, endocrine therapy alone can be considered after core needle biopsy.[15,16] However, for the majority of older women with early breast cancer and life expectancy > 5 years, treatment options should be tailored based on specific risk factors that influence the likelihood of local or systemic recurrence.

The patient presented in case 1 has an excellent performance status, minimal comorbidity, and a life expectancy that likely exceeds 10 years. Unfortunately, her tumor is moderately positive for estrogen receptor and has significant risk for both local and systemic recurrence with high tumor grade. This patient's estimated IBTR risk is > 15% and her estimated systemic relapse risk is > 20%. Whole breast radiotherapy combined with endocrine therapy would be recommended.

Case 2 presents a patient with moderate comorbidity but a good performance status and a life expectancy of at least 5 years. She has a favorable breast cancer that is at low risk for systemic recurrence. Her dominant recurrence risk is local. To reduce this risk, either radiation therapy or endocrine therapy is appropriate, as either approach would be expected to result in an IBTR risk of less than 10% at 10 years. The decision between endocrine therapy and radiation therapy should be based on potential treatment-related adverse effects, as well as patient preference. As this patient has chronic obstructive pulmonary disease, any consideration of whole breast radiotherapy would need to include an assessment of her thoracic anatomy and potential irradiated volume of lung in order to minimize the risk of pneumonitis and compromised lung function. An alternative to whole breast radiation therapy is APBI, as minimal lung tissue is irradiated with most partial breast irradiation techniques. With respect to endocrine therapy, she has mild to moderate arthritis, which may be exacerbated if she is given an aromatase inhibitor. This patient was offered the choice of an aromatase inhibitor, hypofractionated whole breast radiation therapy, or APBI. After a comprehensive discussion of options, she elected endocrine therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Darby S, McGale P, Correa C, 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 randomized trials. Lancet 378:1707-1716, 2011
2. Schonberg MA, Marcantonio ER, Li D, et al: Breast cancer among the oldest old: Tumor characteristics, treatment choices, and survival. J Clin Oncol 28:2038-2045, 2010
3. Antonini N, Jones H, Horiot JC, et al: Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. Radiother Oncol 82:265-271, 2007
4. Owusu C, Buist DS, Field TS, et al: Predictors of tamoxifen discontinuation among older women with estrogen receptor–positive breast cancer. J Clin Oncol 26:549-555, 2008
5. Henry NL, Azzouz F, Zereunesay D, et al: Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. J Clin Oncol 30:936-942, 2012
6. Whelan TJ, Pignol JP, Levine MN, et al: Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 362:513-520, 2010
7. Smith BD, Arthur DW, Buchholz TA, et al: Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys 74:987-1001, 2009
8. Smith BD, Bentzen SM, Correa CR, et al: Fractionation for whole breast irradiation: An American Society for Radiation Oncology (ASTRO) evidence-based guideline. Int J Radiat Oncol Biol Phys 81:59-68, 2011
9. Fisher B, Bryant J, Dignam, J, 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 20:4141-4149, 2002
10. Fyles A, McCready D, Manchul L, et al: Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med 351:963-970, 2004
11. 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 351:971-977, 2004
12. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. http://www.nccn.org
13. Soulos PR, Yu JB, Roberts KB, et al: Assessing the impact of a cooperative group trial on breast cancer care in the Medicare population. J Clin Oncol

30:1601-1607, 2012

14. Hughes KS, Schnaper LA, Bellon JR, 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 31:2382-2387, 2013

15. Hind D, Wyld L, Reed MW: Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: Cochrane review. Br J Cancer 96:1025-1029, 2007

16. Wink CJ, Woensdregt K, Nieuwenhuijzen GA, et al: Hormone treatment without surgery for patients aged 75 years or older with operable breast cancer. Ann Surg Oncol 19:1185-1191, 2012

DOI: 10.1200/JCO.2012.48.3875; published online ahead of print at www.jco.org on May 20, 2013

