

Omitting Radiation in Older Breast Cancer Patients

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Abstract

Breast cancer treatment has evolved concurrently with the advancement of personalized medicine, and as such, many patients are receiving less treatment while still attaining the same rate of cure. Along these lines, there is increasing interest in identifying patients who may avoid radiation therapy after breast conserving surgery without compromising outcomes. NSABP B-21 evaluated women with ER+ tumors 1 cm or less at any age; others have assessed women with ER+ tumors up to 4 cm but over age 50; and CALGB 9343 studied women ages 70 and above with ER+, clinical stage 1 breast cancers. All of these studies randomized patients to radiation versus no radiation, and most required tamoxifen. In each study, radiation therapy did not alter survival, although decreased rates of recurrence were reported and were least in older women with smaller cancers. Based on these and subsequent studies, current guidelines suggest that most women ages 70 and above with clinical stage 1, ER+ cancers do not require radiation therapy after lumpectomy, if they receive standard adjuvant hormonal therapy. Younger women with low risk tumors by genomic signatures might also be included in a subgroup that may avoid radiation therapy, and this group is under study. Radiation oncologists are on the verge of joining breast surgeons and medical oncologists in decreasing the cost and morbidity of breast cancer treatment without negatively impacting survival or quality of life.

Introduction

Breast cancer treatment has evolved concurrently with the advancement of personalized medicine, and as such, many patients are receiving less treatment while still attaining the same rate of cure. Along these lines, there is now increasing interest in identifying patients who may avoid the cost, morbidity, and inconvenience of radiation after breast conserving surgery without compromising their ultimate outcome.

The trend toward lesser treatment has already been employed

in the surgical and medical management of breast cancer. In medical oncology, it was determined early that patients who are negative derive little benefit from anti-estrogen therapy or oophorectomy.^{1,2} More recently, genomic testing has allowed many patients with low-risk tumors to forego chemotherapy.³ In surgery, it has been clearly demonstrated that many women can undergo lumpectomy (with radiation) instead of mastectomy,⁴ and sentinel node biopsy instead of axillary dissection.^{5,6} In those requiring mastectomy, many can now have their nipple preserved.⁷ While radiation oncology has examined decreasing breast radiation with hypofractionation techniques^{8,9} and partial breast irradiation,¹⁰ there remains resistance to omitting radiation entirely, even in selected cases.

The acceptance of breast conservation in the 1980s is germane to the radiation discussion. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 was designed to study whether breast conservation was equivalent to mastectomy.^{4,11} Based on the 1985 analysis, lumpectomy with radiation was deemed an acceptable alternative to mastectomy despite the significant rate of ipsilateral breast tumor recurrence (IBTR) after conservation, because survival was no different than with mastectomy.¹² In addition, this study introduced the idea of an acceptable IBTR rate. While survival was the same with or without radiation, the IBTR rate with radiation (7.7% at 5 years) was considered acceptable. The IBTR rate without radiation (27.9% at 5 years) was deemed too high. Thus, the validation of lumpectomy was based on the tolerance of a moderate amount of IBTR below a given threshold. The Eusoma Guidelines¹³ suggest that a 1% per year rate of IBTR is acceptable, which translates to 5% at 5 years and 10% at 10 years. Patients and physicians seem to find this threshold acceptable as evidenced by the acceptance of IBTR rates similar to this for women with triple-negative breast cancer,¹⁴ young women,¹⁵ those with high-grade DCIS,¹⁶ and those undergoing preoperative chemotherapy.¹⁷ While IBTR rates have continued to improve for many of these subgroups, conservation was still chosen by most physicians and patients even when the reported rates mirrored these thresholds.

Soon after the initial publication of NSABP B-06, the search began for subgroups that might not require radiation after breast-conserving surgery. In the pre-genomic era, characteristics

chosen were combinations of older age, smaller cancers, and estrogen-receptor positive (ER+) cancers. NSABP B-21 evaluated women with ER+ tumors 1 cm or less at any age¹; Fyles et al, assessed women with ER+ tumors up to 4 cm but over age 50,¹⁸ and CALGB 9343 (Cancer and Leukemia Group B, working with ECOG and RTOG) studied women aged 70 and above with ER+, clinical stage 1 breast cancers.¹⁹ All of these studies randomized patients to radiation versus no radiation, and most required tamoxifen use (though NSABP B-21 also had a ‘no tamoxifen’ arm). In each study, survival was not affected, and radiation therapy decreased the rate of IBTR, although this benefit was least in older women with smaller cancers. Other trials, such as PRIME 2 (Postoperative Radiotherapy in Minimum-Risk Elderly), have subsequently been published with similar results.²⁰ It is important to note that overall survival was included in the pre-specified analyses of these studies, although information regarding the statistical power to detect differences was not provided for most of them, as the analyses focused on the primary endpoints related to recurrence.

CALGB 9343¹⁹ accrued 631 eligible patients between July 15, 1994 to February 26, 1999. The median follow-up at the most recent publication was 12 years. Patient and tumor characteristics were evenly distributed between the two groups (Table 1). Locoregional recurrence was decreased by the use of radiation, with a 10-year rate of 10% in the tamoxifen alone group and 2% in the tamoxifen plus radiation group. Thus, there was a net 8% benefit from radiation in terms of locoregional recurrence. When axillary recurrences were excluded and only IBTR recurrences considered, the net benefit decreased to 7%.¹⁹

However, no additional benefits were identified. Radiation had no impact on survival, distant disease-free survival, or the ultimate rate of breast preservation (as many women who who had a recurrence in the breast after tamoxifen alone were still able to salvage their breast with repeat lumpectomy and subsequent radiation at the time of recurrence). Of note, this study was not powered to prove noninferiority with regard to survival.

These results were compelling and changed clinical practice guidelines. The current National Comprehensive Cancer Network (NCCN) guidelines state that women aged 70 and above with clinical stage 1 ER+ breast cancers may be treated with or

TABLE 1. Select Patient, Tumor, and Surgical Factors From the CALGB 9343 Trial Comparing Radiation Therapy with Tamoxifen Versus Tamoxifen Alone (Without Radiation)

	Radiation Therapy +Tamoxifen N (%)	Tamoxifen N (%)
Total Treated	317	319
Age ≥75 years	176 (56%)	172 (54%)
ER+	313 (99%)	313 (98%)
Tumor size ≤2 cm	310 (98%)	313 (98%)
No axillary dissection	195 (62%)	200 (63%)

ER indicates estrogen receptor.

without radiation.²¹ This change propagated into most quality measures (eg, Commission on Cancer, American Society of Clinical Oncology Quality Oncology Practice Initiative, and National Accreditation Program for Breast Cancer), each of whom changed the quality measure requiring radiation after lumpectomy for all patients to now apply only to women less than 70 years old. Unfortunately, this approach has been slow to disseminate into clinical care.^{22,23}

Some have criticized the CALGB 9343 study, suggesting that while the study is true for many patients, it may not apply to those who are healthy.^{24,25} These critics may have overlooked the fact that most women in this study lived longer than would have been predicted for a group of women of comparable age, with more than 50% still alive at 12 years median follow-up.¹⁹ This study accumulated healthier women, and with a longer life expectancy, than an average group of women that age. Thus, poor health does not appear to explain these results, and these data apply to healthy older women.

Some suggest that while this study may be true for many patients, it may not apply to women with high-grade cancers, high-risk genomic scores, HER2 positive, and possibly other subgroups.^{24,26} However, there are no data to support these assertions, and yet many older women receive radiation due to these biases. Critics also contend that the 4% IBTR at 5 years and 9%

TABLE 2. Ipsilateral Breast Tumor Recurrence Rates at 5 Years From the Initial Publications

Study/Radiation Technique	Ipsilateral Breast Tumor Recurrence Rates at 5 years	
	No Radiation	Whole Breast Irradiation
CALGB 9342 ¹⁹	4%	1%
	Partial-Breast Irradiation	Whole Breast Irradiation
Accelerated partial-breast irradiation ¹⁰	4.0%	1.8%
Targeted intraoperative radiotherapy ³³	3.3%	1.3%
Electron intraoperative radiotherapy ³⁴	4.4%	0.4%

IBTR at 10 years in CALGB 9343 are not acceptable.^{25,26} This criticism is interesting, as many breast cancer clinicians accept a similar rate of IBTR in patients receiving intraoperative or partial-breast irradiation (Table 2). The rates of IBTR in high-risk women getting whole breast radiation, in low-risk women not getting radiation, or in low-risk women getting partial breast radiation are acceptable, because we are moving away from the conflation of IBTR, which is accepted and expected in some cases after conservation, with distant recurrence, which is deadly. The acceptance of a finite level of IBTR made breast conservation possible, and a similar recognition is now circulating into the radiation field with the acceptance of conservation without radiation, or with less radiation, in select cases.

The outcome of CALGB 9343 was likely a result of the fact that older women tend to have less aggressive cancers that are more responsive to endocrine therapy.²⁷⁻²⁹ The results likely had less to do with age and more to do with the tumor itself. This has been strongly suggested by others who studied IBTR in younger individuals. For example, in a study of 151 women aged 60 and above with tumors <2 cm, grade 1 or 2, and luminal A subtype, the 10-year rate of IBTR was 1.3% with tamoxifen versus 5% with tamoxifen plus radiation therapy.³⁰

The PRECISION Trial (Profiling Early Breast Cancer for Radiotherapy Omission) builds on this work,³¹ using genomic profiling to limit the use of radiation in a subgroup of women that would likely derive little benefit. In this single-arm study, patients who are ER+, PR+, HER2 negative, grade 1 or 2, and low risk by the Prosigna genomic assay, will be eligible for endocrine therapy without radiation. This study will show a finite rate of IBTR, and the investigators hypothesize that this rate will be acceptable (defined as acceptable if the upper limit of the 95% confidence interval for 5-year locoregional recurrence is below 5%).

We are now moving into an era where the cost of medicine must be contained, and the actual benefit of each therapy must be weighed carefully against cost. Radiation for women aged 70 and above with clinical stage 1, ER+ cancers is expensive and has minimal benefit. These women have much greater risk to their lives and well-being from other causes, with 94% of women who died in CALGB 9343 dying of something other than breast cancer.¹⁹ It is time to consider whether healthcare dollars are better spent on other more deadly aspects of their health rather than on radiation.

This will have implications for the financial status of radiation departments. Konski et al recently reported that the change to hypofractionation in breast cancer radiation will cause a per-case marginal reduction in reimbursement of \$4,297.³² A similar analysis needs to be done for omitting radiation in older women, where the loss of revenue will be many times that amount, and the financial impact on radiation oncology departments will be profound. Fortunately, this may become more palatable as we move away from fee-for-service models and move towards accountable care and value-based medicine.

In summary, most women aged 70 and above with clinical stage 1, ER+ cancers do not need radiation therapy after lumpectomy. Furthermore, studies regarding the use of genomic signatures in younger women with low-risk tumors might ultimately demonstrate an additional subgroup that may avoid radiation therapy. Radiation oncologists are on the verge of joining breast surgeons and medical oncologists in decreasing the cost and morbidity of breast cancer treatment without negatively impacting survival or quality of life.

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