

Editorial

Treatment deescalation for older women with favorable breast cancers: patient values and shared decision making

Deborah R. Smith, MD¹ and Silvia C. Formenti , MD^{*,1,2,3}

¹Department of Radiation Oncology, Weill Cornell Medicine, New York, NY 10065, United States

²Department of Medicine, Weill Cornell Medicine, New York, NY 10065, United States

³Meyer Cancer Center, Weill Cornell Medicine, New York, NY 10065, United States

*Corresponding author: Silvia Chiara Formenti, MD, Sandra and Edward Meyer Professor of Cancer Research, Professor of Radiation Oncology and Medicine, Chairman, Department of Radiation Oncology, Associate Director for Translational Research, Meyer Cancer Center, Weill Cornell Medicine, Radiation Oncologist in Chief, New York-Presbyterian Hospital, 525 East 68th Street, New York, NY 10065, United States (formenti@med.cornell.edu).

Adjuvant radiation therapy following breast-conservation surgery halves local recurrence rates while modestly improving breast cancer-specific survival for early-stage breast cancers.¹ Both increased uptake and technologic advancements in radiographic screening for breast cancers over the past 20 years have facilitated earlier diagnosis producing a leftward stage shift.^{2,3} Concurrently, local recurrence rates have also declined because of a combination of modern surgical techniques and widespread adoption of adjuvant endocrine therapies, fueling interest in therapeutic de-intensification among women with favorable clinicopathologic features, particularly surrounding omission of adjuvant breast radiotherapy. While radiation therapy effectively reduces local recurrence rates, interest has grown in exploring radiation treatment omission because of established risks to adjacent normal tissues, including local symptoms such as breast pain, breast swelling, late fibrosis and adverse cosmesis, radiation dermatitis, hyperpigmentation, brachial plexopathy, cardiopulmonary effects, and small but real risks of radiation-induced secondary malignancies.⁴

Specifically among older women, deferring postoperative radiation therapy has become widely accepted as an appropriate option for patients willing and able to commit to long-term endocrine therapy based on the landmark CALGB 9343 and PRIME II trials, which both demonstrated absolute 10-year locoregional recurrence rates of 10% and 9.5%, respectively, which fell to only 2% and 1% with the addition of adjuvant radiotherapy among tamoxifen-treated women.^{5–6} Several trials including DEBRA, EXPERT, IDEA, and LUMINA are currently investigating whether this paradigm can be safely extrapolated among younger women with favorable breast cancers based on tumor biology and molecular phenotypic profiling.^{7–10}

Expanding on PRIME II and CALGB 9343, Palmer and colleagues¹¹ provide further longitudinal data on local recurrence rates and prognosis following omission of postoperative radiation therapy among older women receiving long-term endocrine therapy. The authors conducted a single-arm prospective phase II trial among 601 women aged 65 years and older who received

6 years of physician's choice endocrine therapy without radiation treatment for hormone receptor-positive T1N0 breast cancers. Patient-reported medication adherence was 86.6%, with approximately 90% of women receiving tamoxifen. Reassuringly, the authors observed cumulative 10-year local recurrence, contralateral breast cancer incidence, and overall survival rates of 5.5%, 4.5%, and 83.1%, respectively, with more than 99% 10-year breast cancer-specific survival.

Incidentally, in the original PRIME I trial examining radiation treatment omission, receipt of adjuvant radiation therapy among older women did not compromise either functionality or overall quality of life.¹² Despite transiently increased fatigue and persistently increased local breast symptoms, patients who received radiation ultimately experienced less anxiety about recurrence. While cosmetic results were predictably better among those who had not received radiation therapy, this was not meaningfully important to many patients. Prospective patient-reported outcomes from a multicenter real-world study indicated that older patients also often feel less bothered than younger women by posttreatment local breast symptoms.¹³

While this trial represents another valuable contribution supporting omission of adjuvant radiotherapy among highly motivated older women with favorable hormone receptor-positive breast cancers who have committed to long durations of hormonal therapy, we believe that shared decision making remains essential toward truly personalizing treatment recommendations. Importantly, physician biases must be mitigated by a dispassionate discussion of data to empower the patients to choose their preferred treatment approaches.

Currently, it remains uncertain whether all women require hormonal therapy to help prevent distant metastases and reduce breast cancer mortality during the modern era. Multiple trials including BASO II, GBSG-V, and NSABP B21 did not suggest elevated distant metastases or compromised survival among women with early-stage breast cancers following adjuvant radiation treatment when omitting tamoxifen.^{14–16} Accordingly, longitudinal survival benefits from endocrine therapy for favorable

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Table 1. Randomized clinical trials demonstrating improved local control following adjuvant radiation therapy after breast-conservation surgery among early-stage breast cancer patients treated with hormonal therapy

Study	N	Age cutoff, y	Cohort	Hormonal therapy	Treatment arms	Landmark	Outcomes
CALGB 9343 ⁵ (Hughes et al., JCO 2013)	636	70 and older	T1N0, estrogen receptor positive	Tamoxifen (5 years)	RT vs no RT	10 years	Local recurrence: 2% vs 10% ($P < .001$)
PRIME II ⁶ (Kunkler et al., NEJM 2023)	1326	65 and older	Tumor <3 cm, N0, estrogen receptor positive	Tamoxifen (5 years)	RT vs no RT	10 years	Local recurrence: 9.5% vs 0.9% ($P < .001$)
NSABP B21 ¹⁶ (Fisher et al., JCO 2002)	1009	None	Tumor <1 cm, N0	Tamoxifen (5 years)	RT vs tamoxifen vs RT/ tamoxifen	8 years	Local recurrence: 2.8% tamoxifen /RT, 9.3% RT, 16.5% tamoxifen ($P < .001$)
BASO II ¹⁴ (Blamey et al., 2013)	1135	Younger than 70	T1N0, grade I, no lymphovascular invasion	Tamoxifen (5 years)	2 x 2 factorial design (RT/ tamoxifen)	10 years	Local recurrence: 17% breast-conservation surgery, 7% breast-conservation surgery/RT, 7% breast-conservation surgery/ tamoxifen, 0% breast-conservation surgery/ tamoxifen /RT ($P < .001$)
GBSG-V ¹⁵ (Winzer et al., 2010)	361	45-75	T1N0, grade I-II, hormone receptor positive, no lymphovascular invasion	Tamoxifen (2 years)	2 x 2 factorial design (RT/ tamoxifen)	8 years	Event-free survival: 48% breast-conservation surgery, 78% breast-conservation surgery/RT, 78% breast-conservation surgery/ tamoxifen, 78% breast-conservation surgery/ tamoxifen /RT ($P < .0001$)
PMH Toronto ²⁷ (Fyles et al., 2004)	769	50	T1-T2 (median = 1.4 cm)	Tamoxifen (5 years)	RT vs no RT	8 years	Local recurrence: 3.5% vs 17.6% ($P < .001$)
ABCSG ²⁸ (Potter et al., 2007)	869	None	Tumor <3 cm, grade I-II, hormone receptor positive	Tamoxifen/ anastrozole (5 years)	RT vs no RT	5 years	Local recurrence: 2.1% vs 6.1% ($P = .002$)

Abbreviation: RT = radiation therapy.

early-stage breast cancers remain less clear in the era of modern surgical techniques, and older women especially may be less likely to manifest possible survival benefits amidst competing medical comorbidities.

Meanwhile, many women experience nontrivial side effects from tamoxifen and aromatase inhibitors including fatigue, insomnia, headaches, malaise, weight gain, dysphoria, mood changes, nausea, hot flashes, and sexual dysfunction that can significantly impact quality of life. Although aromatase inhibitors avoid the elevated risks of thromboembolism and endometrial cancer associated with tamoxifen, they confer greater risks of cardiovascular morbidity, arthralgias, myalgias, and osteoporotic fractures.¹⁷⁻²⁰ As a result, many patients eventually reduce, temporarily pause, or discontinue treatment. Early trials described variable compliance rates with hormonal therapy ranging from 69% to 89%, with almost 20% of patients discontinuing medication within 2 years.²¹ Even in PRIME II, where fewer than 70% of women successfully completed 5 years of endocrine therapy, women randomly assigned to omit radiation treatment who discontinued hormonal therapy experienced substantially increased local recurrence risk compared with those who completed recommended tamoxifen (hazard ratio = 4.66, 95% confidence interval = 1.77 to 1.25).⁶ Real-world medication adherence

is likely lower than desired even among women who complete recommended durations of long-term endocrine therapy compared with patients enrolled in clinical trials, who often receive frequent monitoring, reinforcement of medication adherence and support to enhance compliance.

Real-world evidence confirms that tolerance of endocrine therapy is often challenging. Observed compliance rates are widely variable, averaging around 66%.²²⁻²⁵ In one study where more than 30% of women discontinued endocrine therapy before reaching the recommended 5-year treatment duration, almost an additional 30% who did complete their recommended duration of therapy were nonadherent with medication, and both early discontinuation and medication nonadherence independently predicted mortality.²⁵ Community-treated patients are likely to experience similar patterns of noncompliance, prompting ongoing trials examining de-escalation of endocrine therapy.²⁶

Meanwhile, radiation treatment adherence can be easily monitored and assured. Many randomized trials have confirmed the long-standing value of postoperative radiation toward preventing local recurrences (Table 1).^{5-6,14-16,27-28} Local recurrence importantly remains a top concern for breast cancer patients. Although physicians often place greatest value on survival

benefit, patients frequently prioritize treatment options that minimize any recurrence risk and express strong desire to minimize their likelihood of relapse, even if that requires more intensive treatment regimens associated with greater side effects. Research focused on patient perspectives consistently indicates that early breast cancer patients place substantial value on the benefits of radiation therapy toward preventing local recurrences,²⁹ even prompting some women to opt for bilateral mastectomies as a drastic strategy with the hope of preventing local recurrences of early breast cancers. Long-standing fear of recurrence can dramatically impact well-being and quality of life,³⁰ which may be at least partly alleviated by the knowledge of having pursued all available treatment options to minimize individual risk. Particularly after deciding to omit adjuvant radiation treatment, subsequent breast cancer recurrences may cause guilt, regret, and heightened psychological distress. Older women may also tolerate less well additional procedures required for salvage treatment. For these reasons, some women may consider denying the choice for adjuvant radiation treatment based on age alone as discriminatory.

Accordingly, practicing shared decision making emerges as critical for empowering women to choose their preferred approach. Fortunately, available radiation treatment options have evolved to include partial breast radiotherapy as well as ultrahypofractionated whole breast radiation therapy delivered over only 1 week.³¹⁻³² These shortened courses of radiation align with the goal of therapeutic de-escalation, preserving well-established local control benefits from adjuvant radiotherapy while minimizing logistical burdens and financial strain potentially resulting from longer regimens. Modern techniques, including partial breast irradiation as well as prone positioning and supine breath hold techniques, enable exceedingly low rates of late cardiac and pulmonary side effects through avoidance of normal heart and lung tissue and can be easily implemented in most treatment centers.³³⁻³⁴

Comparative patient-reported quality-of-life data surrounding adjuvant treatment options are rapidly emerging. The Canadian REACT-70 study recently highlighted the central importance of patient preferences surrounding adjuvant treatment options.³⁵ After attempting to randomly assign women with hormone receptor-positive breast cancers to either receive or forego adjuvant endocrine therapy following optimal local therapy, the study was suspended after failing to achieve feasibility outcomes with many women opting away from endocrine therapy altogether, as half of patients declined enrollment and an additional 7.7% opted out after random assignment. Research comparing patient perspectives toward radiotherapy vs endocrine therapy suggests that patients more frequently report negative impact on quality of life from hormonal therapy than radiation treatment (35% vs 14%) and more frequently prefer radiation treatment over hormonal therapy (57% vs 43%).³⁶ Recent interim results of the EUROPA trial, a phase III randomized noninferiority trial comparing quality of life and local recurrence rates following hormonal therapy or postoperative radiation therapy alone among older women, confirmed that endocrine therapy confers more detrimental impacts on global quality of life than radiation treatment with superior 2-year quality of life following radiation treatment alone.³⁷

Especially following the advent of accelerated partial breast irradiation and ultrafractionated whole breast radiation therapy facilitating only 1 week of radiation treatment, clinical decisions must be carefully tailored to each individual patient. Although Palmer and colleagues¹¹ provide additional helpful data

supporting omission among older women strongly motivated to pursue long-term endocrine therapy, shared decision making remains more important than ever based on each individual person's preferences, values, and life circumstances. Ensuring that all patients including older women are fully informed regarding comparative advantages and potential drawbacks of all available treatment options remains essential for protecting patient autonomy and providing patient-centered care.

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Data availability

No new data were generated or analyzed for this editorial.

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