



Omission of adjuvant radiotherapy in early-stage breast cancer: have we identified a subgroup?

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Recognizing the burden, toxicity, and cost associated with adjuvant radiotherapy, investigators have endeavoured to identify a low-risk patient population, in whom the local recurrence risk is sufficiently low, so that radiotherapy can be reasonably omitted. Several randomized trials (1-4) and single-arm studies (5,6) demonstrated unacceptably high local recurrence rates, ranging from mid-teens to high twenties, when patients did not receive adjuvant radiotherapy, even with other favourable features.

To date, only two randomized studies have identified a subgroup of patients who have low local recurrence rates after breast-conserving surgery and endocrine therapy alone: Cancer and Leukemia Group B (CALGB) 9343 (7,8) and PRIME II (9). However, many clinicians continue to have reservations about radiotherapy omission. Patients enrolled on CALGB 9343 were 70 years or older, had T1N0 M0, estrogen receptor-positive, invasive cancers, and were randomly assigned to whole breast radiation or observation, after receiving breast conserving surgery with negative margins and tamoxifen for 5 years. With median follow up of 12.6 years, radiation therapy decreased the risk of locoregional recurrence from 10% to 2% without impacting breast preservation, distant disease-free survival or overall survival. Some consider an 8% absolute gain in locoregional control a small improvement, but others perceive a five-fold difference to be substantial enough to justify treatment. The authors reported that in their patient cohort, 52% had died, but only 6% of these deaths were due to breast cancer. Comorbidities, not specific breast cancer treatments, affected survival in this particular elderly population. Today, nearly two decades after CALGB 9343 trial enrolment, the life expectancy of a 70-year-old woman

is 17.4 years (10). There would be more recurrences and recurrence-related mortality, when patients have longer life expectancy. The PRIME II study included slightly younger patients, aged 65 or older, with shorter follow up of 5 years. These patients had tumors up to 3cm at the longest dimension, hormone receptor-positive, axillary node-negative, resected with clear margins after breast conserving surgery, and were receiving endocrine therapy. Ipsilateral breast tumor recurrence (IBTR) rates decreased from 4.1% to 1.3% by adjuvant radiotherapy, but regional recurrence, distant metastases, and overall survival rates remained the same. The authors concluded that radiotherapy could be omitted for patients with grade 1-2, T1-2 tumors up to 3cm, but cautioned about the generalizability of their results to grade 3 tumors given the small numbers.

Killander *et al.* recently published long term results of the Swedish Breast Cancer Group randomised trial, SweBCG 91 RT (11), in which they randomized 1,187 women with primary T1-2N0M0 breast cancer, after standardized sector resection and axillary dissection, to postoperative whole breast radiotherapy or no further treatment, from 1991 to 1997. After 15 years of follow up, IBTR rates were 23.9% in the control arm and 11.5% in the radiation arm. Breast cancer-specific survival and overall survival were not significantly different between the two groups. The predefined low-risk group included patients aged 64 and above, with tumors that were below 21 mm in size and hormone receptor-positive. The cumulative incidence of IBTR was much better in the radiation arm, 5.3% at 15 years, as compared to 25.9% in the control arm. Other subgroups, determined by age, tumor size, screening detection or receptor status, all had substantial reduction

of risk for IBTR with the addition of radiotherapy (RT). Therefore, they concluded that none of the subgroups in this study were appropriate for consideration of radiotherapy omission.

The strengths of the study were large sample size and long follow up period. This is a large randomized trial on a national basis, including a total of 1178 eligible women. Most IBTR, and the largest reduction of IBTR after radiotherapy were observed during the first 5 years; but, as the authors pointed out, there continued to be a substantial number of IBTR recorded in years 5 to 15, particularly in older patients with small, hormone receptor-positive tumors in the control arm. They argued that, even though molecular subclassification was not performed, small, hormone receptor-positive tumors in older patients tend to be lumina A-like. These have longer median time to IBTR, as compared to HER2+ and triple negative breast cancers, therefore warranting longer follow up to detect recurrence. This is somewhat resonated by comparing local recurrence rates of CALGB 9343 and PRIME II. CALGB 9343 reported 5-year locoregional recurrence rates to be 4% without RT versus 1% with RT (7), similar to 5-year IBTR rates of 4.1% without RT versus 1.3% with RT in PRIME II (9). But with longer follow up period of 12.6 years, CALGB 9343 described locoregional recurrence rates of 10% without RT versus 2% with RT (8).

The authors were insightful at identifying the study's limitations, the crucial one being low rate of endocrine therapy. They explained that adjuvant systemic therapy was not regulated by the study protocol, but was prescribed for stage II patients as a routine practice during that time period. Adjuvant Tamoxifen reduces the risk of in-breast recurrence (1), and its efficacy increases directly with levels of estrogen receptor expression (12). In the current study, 57.6% patients had estrogen receptor-positive tumors, but only 12.5% of these patients received Tamoxifen. These rates were balanced between control and RT groups (11). This explains high IBTR rates observed in this study, especially in the control group, which are in the same magnitude as older studies that reported local recurrence rates between 23% and 27.2% after breast-conserving surgery without RT or endocrine therapy (5,6). Furthermore, high IBTR rates were seen despite the fact that these patients had more extensive surgery, i.e., sector resection instead of lumpectomy. Therefore, unfortunately, the recurrence rates and the degree of RT benefit are not generalizable to patients in present-day practice. It did,

however, reinforce the position that radiotherapy should be recommended for patients who are unlikely to adhere to endocrine therapy, even if they have otherwise low-risk disease.

The method and safety in selecting patients for omission of radiotherapy are still unclear, though we do understand that both patient and tumor profiles are pivotal in this process. With the emerging use of biological and genetic profiling of tumors, researchers today are exploring new tools that allow for the selection of patients with low-risk disease, as determined by tumor biology, as opposed to the classic histopathologic features alone. The LUMINA study is evaluating the risk of local recurrence following breast-conserving surgery and endocrine therapy in low-risk Luminal A breast cancer (13). The IDEA study is assessing locoregional recurrence rates without radiation in select patients who have low Oncotype-DX recurrence score and plan to receive endocrine therapy (14). The PRECISION study is using PAM50, a transcriptional profile of 50 genes, to risk stratify patients with low-risk scores and evaluate the results of radiotherapy omission (15). We will wait for long-term results of these important investigations.

In conclusion, we praise the authors in tackling this topic, providing more insight into de-intensifying treatment for low-risk early-stage breast cancer patients. Changes in practice, especially those that reduce aggressiveness of treatment, are particularly difficult to implement. Decisions regarding adjuvant radiotherapy in low-risk patients depend on an array of tumor and patient factors, and hopefully will become personalized decisions based on new molecular profiling of each individual tumor in the future.

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