Review Article

Pros and cons of radiotherapy omission in elderly breast cancer patients following breast conservative surgery

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Abstract: Breast cancer is a highly prevalent disease worldwide, with adjuvant radiation therapy (RT) being considered standard of care after breast-conserving surgery (BCS). Older patient population can present multiple running comorbidities and less aggressive tumor behavior, and the absolute impact of adjuvant RT on local control can be low. This article aims to review the available literature about the impact of adjuvant RT, discussing characteristics to identify lower risk cases, and advantages and disadvantages of the omission of adjuvant radiotherapy in this group.

Keywords: Breast; cancer; radiation omission

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Introduction

Breast cancer is a highly prevalent disease, with approximately 2.1 million diagnoses estimated worldwide in 2018 (1). Relative survival at 5 years suffers a great variation in the world, ranging from 80% or over in North America, Sweden, Japan, Finland, and Australia to less than 60% in Brazil and Slovakia, and below 40% in Algeria (2).

Since 1985, after the publication of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial, radiation therapy (RT) after breast-conserving surgery (BCS) is the standard of care for patients with early breast cancer, offering improved local control and survival (3).

After this publication, data from NSABP B-21, which included women with small tumors (≤1 cm) randomized to receive isolated tamoxifen (TAM), isolated RT, or TAM associated with radiation after lumpectomy, with no difference demonstrated in distant recurrence or overall survival (OS), but local recurrence (LR) rate with TAM alone were 16.5%, compared with 2.8% in the RT plus TAM group. Forty percent of these patients had unknown or negative estrogen receptors (ERs) tumors, with LR reduced in all subgroups (4).

Breast cancer incidence is higher among older patients, with its peak between 50 and 69 years. Patients older than 70 years of age represent 22% of *in situ* cases, and 31% of invasive cases (5). This elderly population affected by breast cancer usually have running multiple comorbidities and less aggressive tumor behavior (6-8), which can diminish not the relative advantage of adjuvant RT, but the absolute benefit in local control.

Adjuvant RT omission for invasive breast carcinoma

By the time of publication of NSABP B-21, data were already emerging suggesting that there may exist a favorable subgroup of patients in whom irradiation may

not provide meaningful overall benefit. One of the first randomized clinical trials (RCT) evaluating RT omission after lumpectomy was published in 2002 by Fisher *et al.* They evaluated the need for breast irradiation in node-negative women with invasive breast cancers of ≤1 cm, speculating that TAM could be as or more effective than RT in reducing the rate of ipsilateral breast tumor recurrence (IBTR), and by the thesis that both modalities could be more effective than either alone. After lumpectomy, 1,009 women at any age (only less than 20% older than 70 years old) were randomly assigned to TAM (n=336), RT and placebo (n=336), or RT and TAM (n=337). Cumulative incidence of IBTR through 8 years was 16.5% with TAM, 9.3% with RT and placebo, and 2.8% with RT and TAM. RT reduced IBTR below the level achieved with TAM alone, regardless of ER status. Distant treatment failures and OS were not significantly different among the groups. There was a significant reduction in contralateral breast cancer (CBC) when TAM was used (4,9).

Fyles and his Canadian group (10) reported in 2004 the results of their test that included female patients 50 years of age and older randomly assigned to receive TAM alone (383 women) *vs.* TAM plus breast irradiation (386 women) with median follow-up 5.6 years. In this study, women who did not receive radiotherapy had a significantly higher rate of local relapse at 5 years (7.7%) than those who received (0.6%), with no significant differences in rates of distant relapse, OS, or breast cancer death, even with TAM and mandatory free resection margins. However, we can argue that patient selection in this study included large tumors (up to 5 cm in diameter) and did not require a hormone receptor-positive (HRp) status. Considering these factors, another planned analysis, including only ER-positive (ERp) tumors with ≤2 cm, still showed a significant and clinically important reduction in the LR rate in the group receiving radiotherapy; 3.6% in the TAM plus RT group *vs.* 15.2% in the TAM only group after 8 years.

Considering age as an important risk factor, data from the Group B Cancer and Leukemia Study (CALGB) C9343 that evaluated only women over 70 was still. It included ERp tumors ≤2 cm (or those with unknown receptor status), comparing the efficacy of TAM plus RT *vs.* TAM alone. Early results in 2004 suggested that the omission of RT was safe. With a short average follow-up of only 5 years, the incidence of IBTR or regional nodal recurrence was 1% for those receiving TAM plus RT and 4% for patients receiving only TAM. There was no difference in survival, time to distant metastasis or maximum breast preservation rate (11).

Soulos *et al.* (12) analyzed Medicare data until 2007 and reported that the use of RT had little impact, only slightly reducing the risk in this population and that probably with long-term follow-up these results would not be sustained. A long-term analysis was published to address these concerns, with a median follow-up of 12.6 years. At 10 years, 98% of patients receiving TAM plus RT were free from local and regional recurrences, when compared to 90% of those receiving TAM. 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% and 66% in the TAM plus RT and TAM groups, respectively (13).

Following the CALGB C9343 rational, the PRIME II study tested RT omission *vs.* TAM alone in a population older than 65 years old with low-risk features (HRp, axillary node-negative, T1–T2 up to 3 cm at the largest dimension, and clear margins; grade 3 tumor histology or lymphovascular invasion, but not both). Between Apr 16, 2003, and Dec 22, 2009, 1,326 women who had BCS and were receiving adjuvant endocrine treatment, were randomly assigned to either whole-breast RT or no RT. After a median follow-up of 5 years, IBTR was 1.3% in women assigned to whole-breast RT and 4.1% in those assigned to RT omission. No differences in OS, regional recurrence, distant metastases, CBCs, or new breast cancers were noted between groups (14).

As can be seen, several studies have suggested that possibly older women with small tumors that express ERs and will be treated with anti-hormone therapy are part of a favorable subgroup of patients where breast irradiation does not provide a relevant overall benefit. However, an important criticism to be made of PRIME II, CALGB C9343 and similar studies is that the ipsilateral breast recurrence rate in the radiation omission group is relatively high compared to the group of women receiving RT (15).

Also, regarding locoregional control, a meta-analysis with 2,387 patients evaluated data on axillary recurrences for older women after 5 years follow-up (13,14,16). The combination of adjuvant TAM plus RT reduced axillary recurrence rates when compared to the use of TAM alone [relative risk (RR): 0.28, 95% confidence interval (CI): 0.10–0.81, P=0.02; 2,287 patients] with a number needed to treat (NNT) of 116 to avoid one axillary recurrence in 5 years. When we evaluated the subgroup analysis of these two studies, we found that both had low proportions

of axillary lymph node dissection (ALND): PRIME II with 22% ALND and CALGB C9343 with 36%. In this subgroup the low proportion of ALND did not cause statistical difference in axillary recurrence rates with the association of RT (9).

Even with this statically difference in locoregional control, it has to be considered the real clinical benefit of the RT addition in a population of old patients with competing comorbidities. In the CALGB C9343 study, only 21 (6.7%) of 313 deaths were due to breast cancer, and in PRIME II, only 12 (13.5%) of 89 deaths were caused by the disease (12,17,18). Beyond that, all other endpoints (OS, distant metastases, CBCs, or new breast cancers) did not differ between the groups.

It's interesting to note that despite the evidence of an acceptable low-risk of cancer mortality in a selected group, there's a reluctance to de-escalate therapy. RT rate utilization modestly decreased following the publication of CALGB C9343. Many factors seem to be associated with the physician decision on omitting RT in elderly women. The strongest predictors are advanced patient age, high comorbidity score, and low-grade disease (19,20).

The literature assessing the impact of RT on quality of life in elderly patients is limited, as studies do not correlate its adverse effects with its impact on lifestyle. Older women may also face difficulties in accessing treatment, such as reduced mobility, transportation limitations, and other social supports that were not mentioned in these studies (21).

Adjuvant RT omission for ductal in situ breast carcinoma (DCIS)

DCIS consists of a neoplastic tumor confined to the ductal system of the breast, without evidence of invasion of the lamina propria. It is a precursor lesion to invasive ductal carcinoma.

There are at least 4 reported RCTs of surgery resection *vs.* surgical resection plus RT for DCIS (22-25), and one meta-analysis of these trials, which shows a risk reduction of ipsilateral breast event in 10 years by 15.2% (26).

Several studies have tried to identify patients with favorable tumor characteristics in whom maybe RT could be avoided because of low recurrence rates, and derived from that were created score systems and nomograms to stratify these patients. One of note is the Van Nuys Prognostic Index (27) a scoring system that uses pathologic characteristics as tumor size, tumor grade, presence or absence of necrosis and margins status to try to predict recurrence rates. Another tool that can be used to aid the decision to offer adjuvant RT is the Memorial Sloan Kettering Cancer Center online nomogram to predict LR for DCIS (28).

One of the goals of BCS is to offer a good cosmetic outcome. Adjuvant RT for DCIS has no impact on OS, only in local control, and avoiding irradiation can lead to higher taxes of mastectomy (29).

Future and decision-making tools

Throughout the last decade there has been a growing interesting on the evidences that early-stage breast cancer represents a heterogeneous group of diseases defined by unique molecular subtypes that should, in theory, be treated in a more personalized way. However, the focus attention has been on the systemic treatments and risk of distant disease. Recently, some aspects correlating the impact of subtype on LR has also been appreciated (30).

According to these concepts, some open studies are testing whether a subset of patients can actually have a sufficiently low-risk of regional local relapse (RLR) in the absence of RT that justifies omission after BCS. Part of these studies suggest that high-tech genomic assays may be useful in predicting the risk of RVL for women undergoing BCS. For example, researchers such as Mamounas *et al.* (31) demonstrated that the risk of RLR is highly associated with risk groups of 21 recurrence genes (Oncotype-DX) in ERp breast cancer TAM-treated patients with either node-positive or node-positive (32).

Some ongoing trials are committed to demonstrate the influence of molecular subtypes and their genomic assays on the locorregional recurrence (LRR) (*Table 1*). The IDEA study, led by the University of Michigan, is a multicenter prospective cohort aiming to test for RT omission after BCS. The population tested includes patients with stage I unifocal disease, HRp, HER2–, aged 50 to 69 years and with an Oncotype-DX recurrence score (RS) ≤18 (33). PRECISION is a study led by Dana Farber-Brigham and Women's Hospital, which included, in a prospective cohort, patients with stage I unifocal disease with ERp, ages 50 to 75 and a Prosign PAM50 score less than 40 (34). Another study is the EXPERT trial, which uses the PAM50-based Prosigna test as a baseline, recruiting women with biologically low-risk luminal A stage I breast cancer aged ≥50 years. The primary endpoint is LR after BCS at 10 years and they will be randomized to RT plus hormone therapy *vs.* hormone therapy alone (30,35).

Table 1 Ongoing studies evaluating hormone therapy alone after BCS for selected biologically low-risk tumors with genomic assays"

Study	Age	Cohort	Patients profile	Genomic signature
IDEA	50–69	Prospective multicenter cohort	BCS, stage I with pN0; negative margins	Oncotype-DX RS (≤18)
PRECISION	50–75	Prospective multicenter cohort	BCS, stage I with pN0; negative margins; no grade 3	PAM50 low-risk score
EXPERT	≥50	Prospective randomized study	BCS, stage I with pN0; negative margins, biologically low-risk luminal A	PAM50 low-risk score

BCS, breast-conserving surgery; RS, recurrence score.

As the results of most of these trials will not be available in the immediate future, nomograms can be used to guide the daily practice and shared decision with the patients. One of the most solid ones was designed at MD Anderson Cancer Center using Surveillance, Epidemiology, and End Results—Medicare data to identify 16,092 women age 66 to 79 years treated with BCS between 1992 and 2002. This useful tool predicts 5- and 10-year mastectomy free survival among older women with early breast cancer using readily available clinicopathologic factors and can aid individualized clinical decision making by estimating predicted benefit from RT (36,37).

Conclusions—pros and cons of RT omission

Old women with low-risk breast cancer is a group of patients with excellent prognoses. The question is what kind of adjuvant treatment after BCS will guarantee this excellent outcome with less physical, social, emotional and financial cost.

Potential advantages of avoiding adjuvant RT treatment are:

- Absence of radiation treatment related acute and chronic toxicities;
- Lower health care costs.

Potential disadvantages of avoiding adjuvant RT treatment are:

- Increased RR of local cancer recurrence and breast cancer mortality;
- Lower cosmetic outcome (bigger resection to achieve clear adequate margins, less local control can translate into more future mastectomies).

The key to avoid overtreatment in these women is to identify the very low-risk cases of *in situ* or invasive carcinomas, using biological, clinical and histological markers of low-risk, combined to an individualized evaluation of competing comorbidities, properly selecting patients who could be safely avoided WBRT following BCS.

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