



Can elderly patients with low-risk breast cancer benefit from radiotherapy?

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Abstract: There are few trials published on treatment in elderly women with low-risk breast cancer. Although the clinical behavior is like younger patients, there is a tendency to undertreat them, which may lead to an increase in the risk of local relapses and decrease their survival. The local recurrences omitting adjuvant treatment (tamoxifen or radiotherapy) after breast conserving surgery (BCS) even in low-risk patients is high, reaching up 20%, which is unacceptable. Although tamoxifen and radiotherapy seem to have a similar effect in reducing local recurrence with equal overall survival, the combination of both achieves the maximum benefit with local relapses of less than 2%. In recent years two studies have been published and were designed specifically for elderly patients. The CALGB 9343 and the PRIME II trials recommend omitting radiotherapy in patients with low-risk tumors treated with BCS and tamoxifen based on a similar survival, but with an increase in local relapses when radiotherapy is omitted, 10% at 10 years *vs.* 2%. There is no basis to ensure that a treatment with tamoxifen has less toxicity in this group of patients who are usually poly-treated, and it seems that treatment compliance is much lower than expected. The decrease in the number of sessions in external radiotherapy with hypofractionation and accelerate partial breast irradiation, especially intraoperative radiotherapy (IORT) with a single session, makes this recommendation very controversial. Elderly patients may benefit from radiation therapy after BCS.

Keywords: Breast cancer; elderly; radiotherapy; intraoperative radiotherapy (IORT); tamoxifen

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Introduction

Breast cancer therapy is developing towards individualized treatment, trying to maintain efficacy with the least aggressive treatment possible. After the introduction of breast-conserving surgery in the 1980s (1), data was updated in 2002 (2) and demonstrated the equivalence between mastectomy and breast conserving surgery (BCS) with radiotherapy. Since then, techniques have been evolving towards less intensive treatments such as accelerated partial breast irradiation (APBI) and intraoperative radiotherapy

(IORT) for breast cancer. More than 40% of patients with breast cancer are diagnosed after 65 years of age (3). Conversely, as age increases, the probability of performing conservative treatment of breast cancer decreases at stages I and II, sentinel lymph node in N0, and radiotherapy, especially in patients over 80 years old decrease (4).

Breast cancer tends to present with less aggressive characteristics as age increases (5), including greater expression of estrogen receptors, lower proliferation rate, normal *p53*, and absence of expression of the epidermal growth receptor and *c-erbB2*. Older patients with small

tumours and node-negative axilla have a life prognosis similar to the general population according to the Surveillance, Epidemiology, and End Results (SEER) data (5), so treatment is unlikely to have an impact on survival.

A recently published trial, the CALGB 9343 (6,7), suggests that radiotherapy can be omitted in low-risk patients aged 70 years or older undergoing adjuvant treatment with tamoxifen, based on the premise that five years of tamoxifen is better than a course of radiotherapy.

This article reviews these recommendations, as well as the possible benefit of radiotherapy, especially IORT in this group of patients.

Local recurrences after conservative treatment without adjuvant treatment

The percentage of local relapses when radiotherapy is omitted in low-risk patients is not negligible, reaching up to 20.7% in a study by the German Breast Cancer Study Group (GBSG) (8), with relapses extending beyond 5 years (Table 1).

Relapse risk factors have been identified for N0 patients, such as age, size, tumour type, hormone receptors and tumour grade (14). Both the GEC-ESTRO (15) and the ASTRO (16) have identified a subgroup of patients with low risk of local relapse suitable for partial breast irradiation (Table 2).

Holli *et al.* randomized 152 patients (10) comparing lumpectomy alone *vs.* lumpectomy plus radiotherapy without tamoxifen. In both groups, were included patients between 40 and 76 years with low-risk tumours less than 2 cm N0. In local recurrences, they were 7.1% *vs.* 18.1% favourable to radiotherapy, without differences in overall survival.

In the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (14) that included 10,801 patients, of which 1,340 were older than 70 years, radiotherapy shows a benefit at 10 years in relapses of breast cancer in any location (local and distant), with 8.8% for the BCS + RT group *vs.* 17.7% for BCS without RT. This suggests that for every four relapses prevented, one life could be saved.

Randomized trials in older patients with low-risk tumours, comparing BCS with tamoxifen *vs.* BCS with radiotherapy and tamoxifen

Only two specific trials have been realized for patients over

65 years. In 2004 (6), the Cancer and Leukaemia Group B (CALGB) published randomized trial results in 636 patients aged 70 years or older, comparing low-risk patients treated with BCS with adjuvant tamoxifen *vs.* tamoxifen plus radiotherapy. At 5 years, recurrences were 1% for combined treatment and 4% for tamoxifen alone, $P < 0.001$, without differences in survival or mastectomy, concluding that radiotherapy can be safely omitted in this group of patients. In 2013, this same group, CALGB 9343, published results at 10 years of follow-up (7), showing that local recurrences continue to appear beyond 5 years, reaching 10% for the tamoxifen group *vs.* 2% for the combined tamoxifen plus radiotherapy group. There was no difference in overall survival or in salvage mastectomies. It was noted that by omitting radiotherapy, local recurrences continue at a rate of 1% per year.

The PRIME trial II (9) includes 1,326 patients aged 65 years or older with tumours smaller than 3 cm treated with lumpectomy; the randomization was adjuvant treatment with tamoxifen *vs.* tamoxifen plus radiotherapy. Local recurrences at 5 years were 1.3% *vs.* 4.1% favourable to combined treatment. There were no differences in overall survival. These results are very similar to those observed in CALGB 9343 (6,7).

Non-randomized trials in patients older than 70 years BCS *vs.* BCS plus radiotherapy

Martelli *et al.* (11) performed a retrospective study of 627 T1-T2 patients, N0, treated with BCS or BCS plus radiotherapy. At 15 years of follow-up, found no differences in local recurrence, metastasis, cancer mortality or overall survival in patients with pT1. In patients with pT2, local recurrences were 14.6% for patients without radiation therapy *vs.* 0.8%, $P = 0.004$, for patients with radiotherapy. There were no differences in overall survival or cancer mortality. Patients with positive estrogen receptors also received tamoxifen. The patients were treated with quadrantectomy, which perhaps explains the equality of results in patients with T1.

Randomised trials comparing BCS and radiotherapy *vs.* BCS and hormone therapy

Several randomized trials have been realized that set out to analyse the benefit of radiotherapy and hormone therapy in the conservative treatment of low-risk breast cancer (T1-T2 N0). Two trials include BCS as a control group

Table 1 Local relapse in patients with BCS with and without radiotherapy

Trial	Patients (n)	Age (years)	T (cm)	Follow-up (years)	RT	No RT
CALGB 9343 (7)	636	≥70	≤2	10	2%	9%
PRIME II (9)	1,326	≥65	≤3	5	1.3%	4.1%
GBSB Group (8)	347; 186>60 y	≤75; 53.6%>60	≤2	9.9	Overall 7.4%; only RT 9.5%; RT +Tmx 5.3%	20.7%; Tmx 7.5%
Holli <i>et al.</i> (10)	152	≤76	≤2	6.7	7.1%	18.1%
Martelli <i>et al.</i> (11)	627	≥70	≤3	15	T1 8.1%; T2 0.8%	T1 8.1%; T2 14.6%
BASO II (12)	1,171	<70	≤2	14	Overall 3.9%; only RT 8%; RT + Tmx 2%	22%; Tmx 8%
NSABP 21 (2)	1,009	49%≥60	≤ 1	8	Only RT 9.8%; RT + Tmx 2.8%	Tmx 16.5%
Fyles <i>et al.</i> (13)	769	>50; 325 P>70	≤5	5.6	RT + Tmx 0.6%	Tmx 7.7%

BCS, breast conserving surgery; RT, radiotherapy; Tmx, tamoxifen.

Table 2 ASTRO and GEC-ESTRO recommendations for accelerate partial breast irradiation

Clinicopathological features	Suitable for ASTRO (16), including IORT with electron beam [†]	Low risk for GEC-ESTRO (15), limited to the multicatheter BT technique
Age	≥50 years	≥50 years
Histology	IDC, mucinous, tubular, colloid no EIC or LVI	IDC, mucinous, tubular, colloid, medullary no EIC or LVI
Margins	≥2 mm	≥2 mm
Tumor size	Unifocal ≤2 cm	Unifocal ≤3 cm
DCIS	≤2.5 cm [‡]	Not allowed
Nodal status	N0 or N0 (IHC+)	N0
ER status	+	Any
BRCA 1/2 mutation	Absent	No recommendation
Neoadjuvant chemotherapy	Not allowed	Not allowed

[†], IORT with X-ray only should be used within the context of a prospective registry or clinical trial; [‡], margins 3 mm, low or intermediate nuclear grade and screen-detected. EIC, extensive intraductal component; IDC, invasive ductal component; LVI, lymphovascular invasion; ER, estrogen receptor; IHC, immunohistochemical; IORT, intraoperative radiotherapy; BT, brachytherapy.

without adjuvant treatment, the BASO II trial (12) and the GBSG trial (8); this control group is not included neither the NSABP 21 (17) nor in the Fyles *et al.* trials (13). None are designed specifically for elderly patients, although all do include patients older than 60 years, except the BASO II trial (12) in which all patients are under 70 years.

The BASO II trial (12) includes 1,171 patients; the

benefit of radiotherapy is still observed in the presence of hormonal treatment, with local recurrence at 10 years of 22% for surgery alone, 8% for radiotherapy or hormone therapy and 2% when both are associated. Tamoxifen and radiotherapy have the same results in local recurrence, and with equal survival.

The study conducted by the German group GBSG (8)

with 347 patients, 186 patients older than 60 years; local relapse was 20.7% for surgery alone, 9.5% for BCS plus radiotherapy, 7.5% for BCS plus tamoxifen and 5.3% for BCS + RT plus tamoxifen.

The NSABP 21 trial (17) studied 1,009 patients treated with lumpectomy with tumours less than 1 cm to compare tamoxifen alone, radiotherapy plus placebo or tamoxifen and radiotherapy. After 8 years of follow-up, local recurrences were 16.5%, 9.8% and 2.8% respectively. Survival was similar in the three groups. 80% were patients older than 50 years and 490 patients (49%) were older than 60 years.

Similar results were reported by Fyles *et al.* (13) when comparing tamoxifen alone *vs.* tamoxifen plus radiotherapy in 769 patients with T1-T2N0 conservative treatment older than 50 years, of whom 325 were older than 70 years, with local recurrences at 5.6 years of 0.6% *vs.* 7.7% favourable to combined treatment.

The main conclusions regarding local recurrences and survival are:

- (I) local recurrences after BCS without adjuvant treatment are greater than 10% at 10 years;
- (II) both tamoxifen and breast radiotherapy reduce local recurrence;
- (III) the benefits of tamoxifen and radiotherapy are similar;
- (IV) the maximum benefit is obtained by combining tamoxifen and radiotherapy with conservative treatment;
- (V) there are no differences in overall survival.

APBI: IORT

APBI has been shown to be effective in preventing recurrence in patients treated with BCS and low-risk tumours (16). Among these IORT get excellent results in local control.

There are few publications referring to elderly patients, but in none of the published studies have been excluded. There are two randomized trials with IORT, the ELIOT (Electron Intraoperative Radiotherapy) trial (18) and the TARGIT-A (targeted intraoperative radiotherapy) trial (19).

The trial carried out by the Milan-based group, ELIOT, randomized 1,305 patients to BCS plus external radiotherapy, 25 Gy, 2 Gy fraction and boost of 10 Gy *vs.* IORT 21 Gy with electrons, in patients with tumours less than or equal to 2.5 cm aged between 48 and 75 years, with 50% of the patients being older than 60 years and 10% older than 70 years. It included N0-1 patients and patients

with any degree or status of hormone receptors. At 5 years, local recurrences were 0.4% for the external radiotherapy group *vs.* 4.4% for the IORT P<0.0001 group. There were no differences in survival (18). When selecting a group of patients with criteria recommended by ASTRO (16) for APBI, local recurrences were 1.5% and following the recommendations of the GEC-ESTRO (15,20) 1.9%. Of the 35 local relapses, only 4 were in the 62 patients older than 70 years.

The TARGIT-A trial (19) randomized 3,451 patients older than 45 years, N0-1 with any degree and status of hormone receptors: external radiotherapy 50 Gy, 2 Gy fraction *vs.* 20 Gy on the surface of the applicator with X-ray of 50 KV, with the dose at 1 cm being 5–7 Gy. One thousand and two hundred twenty-two patients had a minimum follow-up of 5 years. IORT was randomized into two groups, one administering IORT at the time of the lumpectomy and in the other group, in the weeks later the lumpectomy, with pathological result.

Recurrences at 5 years were 3.3% *vs.* 1.1% favourable to external radiotherapy. In the analysis by subgroup, local recurrences in the IORT group in the time of lumpectomy were 2.1%, with this 1% difference being not significant. The deferred IORT group presented 5.4% of local relapses. Results were also analysed according to hormonal receptor status, showing patients with progesterone receptors positives a local relapse of 0.18%. Another interesting issue of this study (19) is that patients with IORT had a lower overall mortality, 3.9% *vs.* 5.9%, P=0.09, with there were fewer deaths unrelated to breast cancer in the IORT group, 1.4% *vs.* 3.5%, P=0.008. In both trials, the toxicity was not greater than external radiotherapy.

This same group initiated a phase II trial aimed at patients aged 70 years or older, with tumours less than 3.5 cm, N0, TARGIT-E (21) with 3 years of follow-up included in 538 patients, with only 1 relapse (0.18%) being noted.

Discussion

Based on the CALGB 9343 (6,7) and PRIME II (9) trials, the National Comprehensive Cancer Network (NCCN) (22) and the National Institute for Health and Care Excellence (NICE) (23) guidelines, among others, recommended that radiotherapy can be omitted in patients aged 70 years or older with low-risk breast cancer who receive hormonal therapy.

We must make several comments about these trials and recommendations. First, the survival benefit in patients

younger than 70 years with low risk breast tumors, T1 N0, positive receptors, margins greater than 2 mm as demonstrated in the EBCTCG meta-analysis (14) and BASO II trial (12) is minimum. And secondly, the percentage of local recurrence even with tamoxifen is not negligible, 10% at 10 years, a percentage which is considered inadmissible in younger patients.

Meanwhile, the recommendation to administer tamoxifen and omit radiotherapy is very questionable. The BASO II trial (12) showed that the benefit of external radiotherapy and tamoxifen are similar in reducing local recurrence with equal survival. With these results, there is nothing to support that 5 years of treatment with tamoxifen in elderly patients, usually polymedicated, is better than a radiotherapy treatment of one month or less as is the case of hypofractionation. Radiotherapy in healthy elderly patients is well tolerated.

Hershman *et al.* (24) studied a group of 8,769 patients with early breast cancer and found that only 49% of patients received hormonal treatment for the all time of prescription, with those younger than 40 years and older than 75 years being the most likely to discontinue treatment. Moreover, this non-compliance (discontinuation and non-adherence) has effects on the result of the treatment, while reducing survival.

Another argument used to omit radiotherapy is financial. Sen *et al.* (25) studied the cost-effectiveness of external radiotherapy in 18,340 patients in a group of 8,769 patients over 70 years with early breast cancer and treated with BCS, all from SEER program, and concluded that despite the concern for the overtreatment of this group of patients, radiotherapy is cost-effective. Logically, this benefit decreases in patients with short life expectancies and as they get older. This cost-effectiveness increases in IORT (26), which is the preferable treatment in patients with early breast cancer together with hypofractionation.

There are few publications on patients older than 80 years and no randomized trials that study the benefit of adjuvant treatment with early tumours. The tendency is to omit radiotherapy in a greater percentage and recommend tamoxifen alone, although this may result in undertreatment that worsens its prognosis. Bouchardy *et al.* (27), in a retrospective study of patients over 80 years, concludes that more than 50% of patients receive suboptimal treatment compared to patients younger than 80 years (47% vs. 91%), with the best results being patients who are treated with BCS + RT, so undertreatment clearly decreased survival.

In recent years, new radiotherapy treatment techniques have been introduced which have the same results but

considerably shorten treatment time (hypofractionation) and irradiation volume, such as APBI and IORT. The latter are especially interesting because in a single intraoperative session, the recurrences in low-risk group are equivalent to external radiotherapy, as demonstrated both in the ELIOT and TARGIT-A trials (18,19). This makes it especially attractive in this group of elderly patients.

Another important advance in the treatment of breast cancer in elderly patients has been the generalization of hypofractionated treatments following publication of the START-A and B trials (28,29), demonstrating equal effectiveness in a randomized trial between standard treatment (25 fractions of 2 Gy) and hypofractionation (15 fractions of 2.67 Gy, 13 sessions of 3.2 or 3 Gy). Other non-randomized trial (30) with more extreme hypofractionation with 5 fractions of 6.5 Gy one a week, have shown similar efficacy in patients older than 70 years.

With these advances and results published with APBI, particularly IORT and hypofractionation, it is difficult to argue that adjuvant tamoxifen alone is the treatment of choice in older patients with low-risk breast cancer treated with BSC.

Conclusions

There are few randomized trials that analyze optimal treatment in elderly patients with low-risk breast tumours. The behavior of these tumours does not seem very different from tumours of similar risk in younger patients, where neither does the treatment adjuvant to BCS seem to influence overall survival. Local recurrences after BCS without adjuvant treatment are unacceptable for all groups, so it is advisable to perform adjuvant treatment after BCS. Radiotherapy and tamoxifen seem to have a similar effect in preventing local recurrence and survival, so there is not rationale for recommending 5 years of tamoxifen instead of radiotherapy. Radiotherapy, in any of its modalities, especially IORT and hypofractionation, are cost-effective in this group of patients and it is well tolerated.

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