



# Adjuvant radiotherapy for low-risk early breast cancer in elderly women: evidence from randomized trials

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**Abstract:** Breast cancer is the most common cancer pathology in women in the Western world. The median age at diagnosis is 60 years and in the coming decades it is estimated that the number of elderly women affected reaches an important percentage. This aging of the cancer population, associated with its inherent comorbidities and aggravated by the lack of consensus about the most appropriate treatment, make it difficult to administer an effective postoperative treatment in elderly women with a low-risk profile. An exhaustive geriatric evaluation is a sine qua non condition to opt for a specific type of treatment. To date, several options are available such as endocrine therapy (ET) alone, moderate/high hypofractionation and various accelerated partial breast irradiation (APBI) techniques. In this article, we provide information about each of them.

**Keywords:** Breast cancer; elderly; low-risk

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## Introduction

Adjuvant external beam radiotherapy (EBRT) increases local control, disease free survival and overall survival after conservative surgery (1). Furthermore, adding a boost to the tumor bed increases local control in all patients regarding age (2).

In elderly patients with breast cancer, the baseline risk of recurrence is lower than that of younger people, which gives a minor but significant absolute benefit in the administration of radiation, an absolute reduction of 8.9% to 10 years of risk of recurrence (1), probably associated to a

major proportion of luminal cases (3).

In elderly patients with low-risk luminal cancer, the usefulness of adjuvant radiotherapy (RT) would be considered controversial. Several reasons could be taken into account:

- (I) Age: definition of an elderly patient in breast cancer use to be associated to age over 70 years. In those patients, a short to moderate life-expectancy is argued in order to reduce treatment burden for cancers that theoretically, will not be relevant for overall survival.

Two arguments could be considered:

- (i) Breast cancer is diagnosed at a median age of 60 years old and more than 40% of these patients are over 65 (4). In the year 2030, it is assumed that 20% of the population will be over 65 years old, and in the near future, the proportion of elderly women with early breast cancer, will probably grow considerably.
  - (ii) Age alone is not determinant of life expectancy and a complete geriatric clinical evaluation is necessary (5,6). Comorbidities, functional status, cognitive function, nutritional status and polypharmacy use, are associated with survival and toxicity in elderly patients with malignant disease (7,8).
- (II) Despite the advantages of lumpectomy, which involves a less extensive surgical intervention than mastectomy, many women choose to undergo a mastectomy, due to the side effects of whole breast radiotherapy (WBRT) and the burden of treatment, including traveling to a radiation treatment facility for daily treatments for 3–5 weeks (9). Patients would not be able to complete treatments, leading to the underutilization of RT (10,11), which would theoretically entails a detriment to health.
- (III) The risk of cardiac toxicity is another reason that would lead to an underuse of WBRT. Relevant data from WBRT administered between 1958 and 2001 [before intensity modulated radiotherapy (IMRT) treatment], showed a dose-dependent effect of the long-term incidence of cardiac ischemic disease (12). The detrimental cardiac effect of WBRT is strongly related to the survival of patients, being larger in younger ages, begins within a few years after exposure and continues for at least 20 years (12).

### Could adjuvant RT be safely omitted in low-risk early breast cancer elderly patients?

Three randomized trials gave proven evidence that the omission of postoperative RT in advanced-aged women, T1-2 N0 with invasive carcinoma, receiving endocrine therapy (ET) results in higher local recurrence (LR) rates without harm to overall survival (13-15) compared to WBRT + ET.

Hughes *et al.* (13) in the CALGB 9343, randomized 633 patients >70 years, after lumpectomy and lymph node sampling or axillary dissection. After a median follow-up of 12.6 years, the 10-y local relapse rate was 2% for the tamoxifen + RT arm *vs.* 10% (5-fold increase) of the tamoxifen arm alone. There were no significant differences in time to mastectomy, time to distant metastases, breast cancer-specific survival. There were no significant differences in overall survival (67% *vs.* 66%, respectively).

Fyles *et al.* (14) in a similar trial included 769 women >50 years with tumors smaller than 5 cm, negative nodes and with positive hormone receptors. The combined arm of tamoxifen + RT, decreases the rate of local (0.6% *vs.* 7.7%,  $P < 0.001$ ) and regional (0.5% *vs.* 2.5%,  $P = 0.049$ ) recurrence compared to tamoxifen alone, but without significant differences in the rates of distant relapse (4.0% *vs.* 4.5%,  $P < 0.69$ ) or overall survival (91.9% *vs.* 92.4%, respectively).

The PRIME II study (15) randomized 1,326 early breast cancer patients >65 years of age, to receive postoperative RT + ET *vs.* ET alone after breast surgery and axillary dissection. Inclusion criteria included infiltrating tumors, <3 cm, T1-2 N0, free margins and positive hormone receptors. Five-year local relapse was 1.3% for patients undergoing postoperative RT + ET compared to 4.1% (3-fold increase) ( $P = 0.0002$ ) in those not receiving postoperative RT. Survival was similar in both treatment arms (93.9% in both groups).

As a result of the 3 previous studies, there is some controversy suggesting that there is sufficient level I evidence collected in the guidelines of the National Comprehensive Cancer Network (16) and the Royal College of Radiologist-UK (17), which allows to omit RT in elderly patients, who are going to complete 5 years of ET and who have low-risk characteristics, such as infiltrating carcinoma, T1-T2, negative lymph nodes with high expression of hormonal receptors without detriment to overall survival.

In addition, not all the 3 studies were powered for detecting moderate increments in survival induced by adjuvant WBRT. Strong 1A evidence (1) is available demonstrating a life saved in every 4 prevented local relapses. If an 8% local relapse is prevented with adjuvant EBRT at 10-y, a 2% increase in survival at 10-y would be expected.

On the other hand, hormone therapy is not without complications. Several trials have shown that the lack of

compliance with the use of these medications is substantial, with approximately 50% of patients who do not complete 5 years of therapy (18,19). Age is by itself, a factor that affects adherence to treatment (20,21). Musculoskeletal symptoms such as arthralgias, myalgias (22,23) and osteoporosis associated with risk of fractures (24) are side effects of aromatase inhibitors (AI) that can undermine the quality of life of patients, while thromboembolic risk and endometrial cancer are problems to be taken into account, when tamoxifen (22) is used. Survival is similar for both AI and tamoxifen, but the overall risk of relapse is slightly lower with AI (25).

For all this, omitting external RT in this group of patients is not widely accepted, as LR rate is higher in those patients not receiving adjuvant RT. This is not a minor problem for an elderly patient, requiring local treatment, RT, mastectomy or new systemic treatment including, in some cases, chemotherapy.

Due to these arguments, it is necessary, in our opinion, to offer adjuvant RT to elderly patients, as a treatment option that adapts to their current situation, without altering their quality of life and guaranteeing treatment compliance.

## RT

### WBRT

#### Moderate hypofractionation

Accelerated hypofractionation (16,17), has provided logistical and economic advantages, reducing the treatment time from 5 to 3 weeks, maintaining similar local control rates without worsening aesthetics (26). This treatment regimen has been evaluated in 3 large well-designed randomized clinical trials (27-29).

START-A (27) recruited 2,236 women with breast cancer (pT1-3a pN0-1 M0) from 17 centers in the UK, assigned after lumpectomy, to receive 50 Gy/25 fx of 2.0 Gy *vs.* 41.6 Gy/13 fx of 3.2 Gy or 39 Gy/13 fx of 3.0 Gy in 5 weeks. After a median follow-up of 5.1 years, the local-regional tumor relapse rate at 5 years was 3.6% [95% confidence interval (CI), 2.2–5.1] after 50 Gy, 3.5% (95% CI, 2.1–4.3) after 41.6 Gy, and 5.2% (95% CI, 3.5–6.9) after 39 Gy.

START-B (28) was developed at the same time as START-A, enrolling 2,215 patients randomizing to receive 50 Gy/25 fx *vs.* 40.05 Gy/15 fx. Local-regional recurrence

(LRR) at 10 years, did not differ significantly between the group of 40.05 Gy (4.3%) and the group of 50 Gy (5.5%). Late toxicities were less common in the hypofractionated group than in the conventional fractionation group.

Whelan *et al.* (29) randomized 1,234 patients to receive 42.6 Gy/16 fx *vs.* 50 Gy/25 fx, without prescribing boost to the surgical cavity. At 10 years, there was no significant difference in LR (6.2% in the group of 42.6 Gy *vs.* 6.7% in the group of 50 Gy) with better esthetic results.

Moderate hypofractionation was established as the new standard of treatment in breast cancer patients. The shortness of the treatment time would be especially important for elderly patients.

However, 3 weeks of treatment remains a difficult problem for some patients. Weekly hypofractionation (1 fx/week) may be a valid option in those patients with difficulties receiving a treatment with accelerated hypofractionation. Long distances from home to RT centers, comorbidities continue to be the common causes of not carrying out and not completing treatment with ionizing radiation.

#### High hypofractionation

Due to the favorable results obtained with moderate hypofractionation, it was thought to hypofractionated the RT course even more.

The UK FAST trial (30) is a phase III trial, which included 915 patients with early stage, randomized 1:1:1 to 50 Gy/25 fx (control group) *vs.* 30 Gy/5 fx *vs.* 28.5 Gy/5 fx, in 5 weeks after conservative surgery. Whole breast was treated.

In the last revision of the results (31), disclosed in the ASTRO 2018 in San Antonio, severe effects were observed in 13 of the 774 women (1.7%) with follow-up data at 5 years, and 9 of the 392 women (2.3%) with follow-up data at 10 years. No changes or only minor changes in normal tissue were observed in 88% and 86% of women at the 5- and 10-year marks, respectively. Late normal tissue effects were not statistically different between the conventional therapy group and the 5-fx 28.5-Gy group at 5 years or 10 years following treatment. Moderate/severe late effects to normal breast tissue were higher, however, for patients who received the 5-fx 30-Gy regimen. These patients were two to three times more likely to experience moderate/severe instances of breast shrinkage ( $P < 0.001$ ), hardness ( $P = 0.004$ ),

fluid buildup ( $P < 0.001$ ), and spider veins ( $P = 0.02$ ). Among patients on the conventional, daily-fraction arm, physicians observed normal tissue effects in 7.5% at 5 years and 9.1% at 10 years. By comparison, rates for the 5-fx 30-Gy arm were 18.0% at 5 years ( $P < 0.001$ ) and 18.4% at 10 years ( $P = 0.04$ ). These results suggest that 28 Gy delivered into 5 fx in 5 weeks would be equivalent to 50 Gy in 25 fx in 5 weeks. The 10-year local relapse rate for all patients in the trial was 1.3% (95% CI, 0.7–2.3), with only 10 events reported in total, balanced between the treatment groups.

Another attempt to shorten the total time of treatment is the FAST-Forward trial (32). This is a phase III, multicenter, randomised controlled trial that aims to identify a 1 week, 5 fx schedule of curative RT that is at least as effective and safe as the current UK standard 15 fx regimen, used after primary surgery for early breast cancer. Four-thousands one-hundred patients were recruited from different UK sites. Each participant was allocated to one of the following groups: 40.05 Gy/15 fx of 2.67 Gy, 27.0 Gy/5 fx of 5.4 Gy and 26.0 Gy/5 fx of 5.2 Gy. Participants will be followed up for 10 years following completion of RT.

#### *Accelerated partial breast irradiation (APBI)*

Smith *et al.* (33), Huang *et al.* (34) and Fowble *et al.* (35) showed that the majority of ipsilateral recurrences occurred in the same quadrant initially affected, which provided the concept that the irradiation focused to the vicinity of the lesion was adequate to achieve local control, without increasing the toxicity to neighboring organs. APBI would be an appropriate treatment option for a group of patients with early breast cancer after conservative surgery. APBI involves the delivery of high doses per fraction in the lumpectomy cavity, either as a boost or as a single treatment. The use of APBI was included in the most recent guidelines of the National Network of the Comprehensive Cancer Center-NCCN (16).

There are several techniques implemented to perform APBI tested in large, randomized trials, including: external RT, intraoperative radiotherapy (IORT) and interstitial multicatheter brachytherapy (BT). All APBI techniques involve treating a limited and specific volume of breast tissue in a much shorter course than traditional full breast radiation. The American Society of Radiation Oncology (ASTRO) (36), the Group of Curietherapy of the European Society of Radiation Oncology (GEC-ESTRO) (37) have

published consensus statements regarding the different groups of candidate patients for treatment with APBI. ASTRO and American Brachytherapy Society (ABS) (38) have recently updated their guidelines, which results in more open patient selection criteria. From the patient's perspective, the tangible benefits of APBI can be found mainly in improving access to radiation treatment, less travel distance (39), cost reduction, patient compliance, less exposure to RT in normal tissues and improved cosmetic results (40–42) being an ideal option for elderly and frail patients with low-risk tumor disease.

#### **External beam radiation therapy**

Livi *et al.* (43) in a phase III trial conducted at the University of Florence, included 520 patients >40 years in the early stage with tumors <2.5 cm who were randomized 1:1 to whole breast irradiation (WBI) (50 Gy/25 fx + 10 Gy/5 fx to the tumor bed) *vs.* APBI using IMRT (30 Gy/5 fx daily to the tumor bed). The primary endpoint was to evaluate the ipsilateral breast tumor recurrence (IBTR). At a median follow-up of 5 years, the IBTR was 1.5% in both groups. The 5-year overall survival was 96.6% for the WBI group and 99.4% for the APBI group. The APBI group presented significantly better results considering acute ( $P = 0.0001$ ), late ( $P = 0.004$ ), and cosmetic outcomes ( $P = 0.045$ )

Olivetto *et al.* (44) in a randomized trial of APBI, using conformed 3D RT, including 2,135 women, assigning 1,070 to 3D-CRT APBI (38.5 Gy/10 fx twice daily) and 1,065 WBI (42.5 Gy/16 fx or 50 Gy/25 daily fx ± boost irradiation). The primary outcome was IBTR. Secondary outcomes were cosmesis and toxicity. In an interim analysis of cosmetics and toxicity, with an average follow-up of 36 months, an increase in adverse effects was determined in the APBI group compared to the WBRT group evaluated by the nursing staff (29% *vs.* 17%;  $P < 0.001$ ) by patients (26% *vs.* 18%;  $P = 0.0022$ ) and by the physicians (35% *vs.* 17%;  $P < 0.001$ ). Due to the high rates of adverse effects, it would be opted for by other forms of performing APBI.

Rodríguez *et al.* (45) reported the results of a small study that compared the efficacy, toxicity and cosmesis of breast conservation treatment with APBI or WBI using 3D-CRT. One-hundred and two patients were included: 51 patients to WBI (48 Gy in 2 fx daily ± boost) and 51 patients to APBI (37.5 Gy in 10 fx 2 times per day). The mean follow-up was 5 years. No LR was observed. No significant

differences were found in survival rates. The percentage of patients with excellent/favorable results was the same in both groups, but this trial must probably be regarded as under-powered to detect relevant differences between the treatment arms.

### IORT

IORT offers the possibility of a single dose of ionizing radiation inside the surgical cavity, immediately after the lumpectomy. There are two large randomized studies that compared postoperative RT *vs.* IORT.

The TARGIT-A trial (46) is an IORT study of noninferiority, randomized 1:1 of 3,451 patients with early stage breast cancer, distributed in two arms: WBRT  $\pm$  boost *vs.* IORT directed to the tumor bed. There were 379 patients  $>65$  years in the WBRT arm and 441 patients  $>65$  years in the IORT arm. The IORT dose, was administered with the INTRABEAM (Carl Zeiss Meditec, Obereckochen, Germany), a miniaturized linear energy accelerator of 50 kV. The radiation dose was delivered through spherical applicators of different sizes (1.5–5.0 cm in diameter) placed in the cavity surgical. Twenty Gy was administered in a single session for 30 to 45 minutes. The patients of the IORT arm received also EBRT if adverse tumor factors were present in the review of the pathological anatomy. The risk at 5 years of LR was 3.3% (95% CI, 2.1–5.1) for IORT *vs.* 1.3% (95% CI, 0.7–2.5) for EBRT ( $P=0.042$ ). IORT at the same time of lumpectomy (pre-pathology cohort,  $n=2,298$ ) had very similar results to those of EBRT: 2.1% (95% CI, 1.1–4.2) *vs.* 1.1% (95% CI, 0.5–2.5;  $P=0.31$ ). When IORT was deferred to a second breast surgery (post-pathology cohort,  $n=1,153$ ), the difference between the groups was greater than 2.5% [IORT 5.4% (95% CI, 3.0–9.7) *vs.* EBRT 1.7% (95% CI, 0.6–4.9),  $P=0.069$ ]; Overall, mortality from breast cancer was very similar between groups [2.6% (95% CI, 1.5–4.3) for IORT *vs.* 1.9% (95% CI, 1.1–3.2) for EBRT,  $P=0.56$ ] but there were significantly fewer deaths from breast cancer with IORT (1.4% *vs.* 3.5%), attributable to fewer deaths from cardiovascular causes and other cancers. Overall mortality was 3.9% (95% CI, 2.7–5.8) for IORT *vs.* 5.3% (95% CI, 3.9–7.3) for EBRT ( $P=0.099$ ). The complications related to the wound were very similar between the groups, but the cutaneous complications of grade 3 or 4 were significantly reduced with IORT (4/1,720 *vs.* 13/1,731,  $P=0.029$ ).

The other major study comparing postoperative RT *vs.* IORT is the ELIOT trial (47), a phase III trial that randomly assigned 1,305 patients, who were  $\geq 48$  years with tumors  $\leq 2.5$  cm, to a single intraoperative dose of 21 Gy given by electrons (Novac7) or EBRT of 50 Gy WBI plus a 10 Gy bed boost, delivered in 6 weeks. After a median follow-up of 5.8, the 5-year recurrence rates for ELIOT and EBRT were 4.4% and 0.4%, respectively ( $P=0.0001$ ). These higher rates of local failure with IORT are probably related to inadequate coverage of subclinical disease (48). The low-risk ELIOT group had a 5-year recurrence rate of 1.5% (49). Furthermore, the ELIOT group had significantly less skin toxicity (erythema, dryness, hyperpigmentation or itching), but a higher incidence of fat necrosis.

### Interstitial BT

Strnad *et al.* (50), conducted a phase III, randomized, non-inferiority study of APBI with interstitial multicatheter BT in patients with early breast cancer. One-thousands one hundred eighty-four patients were enrolled: 551 patients were randomized to receive EBRT, (96 patients  $>70$  years) and 633 patients to receive APBI, (94 patients  $>70$  years). APBI was administered with high dose rate (HDR) or pulsed dose rate (PDR) BT. For HDR-BT, a total dose of 32 Gy was used in 8 fx ( $8 \times 4$  Gy) or 30.3 Gy in 7 fx ( $7 \times 4.3$  Gy), with fractionation twice a day. PDR-BT administered a total dose of 50 Gy with pulses of 0.60–0.80 Gy/h (one pulse per hour, 24 h/day). After 5 years of follow-up, nine patients treated with APBI and five patients who received complete breast irradiation had a LR. The cumulative incidence of LR was 1.44% (95% CI, 0.51–2.38) with APBI and 0.92% (95% CI, 0.12–1.73) with total irradiation of the breast (difference 0.52%; 95% CI,  $-0.72$  to 1.75;  $P=0.42$ ). Late fourth-degree side effects were not reported. The risk to 5 years of late side effects in grade 2–3 skin was 3.2% with APBI *vs.* 5.7% with total breast irradiation ( $P=0.08$ ) and 5-year risk of grade 2–3 late side effects in the subcutaneous tissue was 7.6% *vs.* 6.3% ( $P=0.33$ ). The risk of severe fibrosis (grade 3) at 5 years was 0.2% with total irradiation of the breast and 0% with APBI ( $P=0.46$ ). These results showed that the APBI performed with HDR-BT multicatheter is not inferior to the EBRT in terms of local control, disease-free survival and overall survival, being a more valid option for older patients.

## Discussion

The choice of treatment for older patients with early stage breast cancer is complex and given the category of public health problem, associated with an increase in life expectancy, it becomes essential to promote treatment consensus strategies; any treatment that is considered convenient, must be administered prior to a comprehensive geriatric evaluation (51). The sole evaluation of the performance status is not enough to opt for a treatment (52). Despite well-known and strongly contrasted data on the efficacy of adjuvant RT after conservative surgery in reducing the rate of LR and increasing cancer-specific survival and overall survival (1), there is an underutilization of RT (9). In places where RT departments are located at long distances from second-level care hospitals, many doctors recommend mastectomy in women with early stage breast cancer. The percentage of mastectomies was observed to be greater in patients older than 70 years than in those younger than 70 years in places with a wide demographic dispersion (9). It was also known that the level of education has a lot to do with the choice of surgical treatment. Women with better levels of education, opted for conservative surgery as opposed to low educational level (11). Another factor to consider is to anticipate the difficulty in administering RT to elderly patients, due to positioning and immobilization in supine or prone, since many of these patients due to joint and rheumatological problems, will find it difficult to complete the course of external RT treatment.

For all the aforementioned problems, it is necessary to: (I) stratify those elderly patients in whom adjuvant RT would be omitted without compromising their clinical outcome; (II) implement RT techniques to replace the long course of treatment, maintaining similar control rates local and toxicity.

Omitting RT in patients belonging to the low-risk subgroup (tumor <3 cm, N<sup>-</sup>, HR<sup>+</sup>, HER2<sup>-</sup>) is associated with a higher risk of LR (13-15). To solve this problem, it is necessary to discuss the treatment alternatives to which elderly patients can be submitted to adjuvant RT without harming their quality of life.

After the publication of the 5-year results of the START trials, most centers in the UK pragmatically adopted the 15-fx program as standard of care, as recommended by the NICE guidelines in 2009 (53). The START pilot trial (54,55), START-A (27), START-B (28) trials and Ontario

trial (29), considered together, present robust evidence that hypofractionation is a safe and effective approach to breast cancer RT. Weekly hypofractionation, delivering one session per week for several weeks (30) or in one week (32) are also effective ways to complete post-surgical RT, saving logistics and economic costs to patients.

The aim of APBI is to allow a good local control by giving a high irradiation dose in a small volume with a small number of fractions. APBI is well tolerated for elderly patients with no detrimental impact on functional autonomy and quality of life (41,42,56).

The multicatheter BT, proved not to be inferior to standard treatment, with respect to the 5-year LR rate (approximately 1% in both groups) and a low importance of all late side effects (around 3% in both groups), confirming that it is a technique to be taken into account in the strictly selected patient (50).

At 5 years of follow-up, noninferiority regarding local control of IORT compared to EBRT was confirmed when TARGIT was administered immediately after lumpectomy. Complications of the surgical wound were similar between the two groups, but there was less toxicity > G3 in the TARGIT group. The most important benefit of TARGIT is that it allows you to complete all the local treatment at the time of your operation with less toxicity, besides saving costs and time for both the health provider and the patient. In our opinion would be considered a more than valid option for elderly patients (44).

External RT, both three-dimensional conformal and IMRT is another way to administer a treatment with APBI, which is easy to perform and is widely available. However, the studies carried out have resulted in a worse rate of adverse effects when compared with full-breast RT, in addition to the studies carried out, it has a low statistical power.

## Conclusions

The benefit of RT after lumpectomy is clear patients with early stage breast cancer, because it improves local control, survival, cancer and overall survival. *Table 1* summarizes the main characteristics of the trials that we mention in this article. In elderly patients, adjuvant RT prevents local relapse and decrease aggressive treatments for relapses. RT through APBI, especially under IORT treatment seems to be the best alternative for this growing group of patients.

**Table 1** Overview description of the randomized trials mentioned in this article

Study	Patients	Elderly (%)	Treatment (dose)	Local relapse 10-y (%)	Adverse cosmesis (%)
Moderate hypofractionation					
START-A (27)	2,236	12.3	50 Gy/25 fx	7.4	42
			41.6 Gy/13 fx	8.8	42
			39 Gy/13 fx	6.3	31
START-B (28)	2,215	11.5	50 Gy/25 fx	5.5	40
			40.05 Gy/15 fx	4.3	30
Whelan <i>et al.</i> (29)	1,234	16.7	50 Gy/25 fx	6.7	29
			42.6 Gy/16 fx	6.2	30
High hypofractionation					
UK FAST (30)	915	15.3	50 Gy/25 fx	0.9	21
			30 Gy/5 fx	1.29	35
			28.5 Gy/5 fx	1.31	24
APBI with EBRT					
Livi <i>et al.</i> (43)	520	22.5	WBI: 50 Gy/25 fx + boost	1.4*	0.8
			APBI: 30 Gy/5 fx	1.5*	0
Olivotto <i>et al.</i> (44)	2,135	88 (>50-y)	WBI: 50 Gy/25 fx or 42.5 Gy/16 fx ± boost	NR*	17
			APBI: 38.5 Gy/10 fx	NR*	35
Rodríguez <i>et al.</i> (45)	102	100 (>60-y)	WBI: 48 Gy/24 fx ± boost	0*	3
			APBI: 30 Gy/5 fx	0*	2
APBI with IORT					
TARGIT-A (46)	3,451	14.9	WBI: 40–56 Gy/15–23 fx ± boost	1.3*	0.7**
			IORT: 20 Gy/1 fx	3.3*	0.2**
ELIOT (47)	1,305	10.6	WBI: 50 Gy/25 fx + boost	0.4*	NR
			IORT: 21 Gy/1 fx	4.4*	NR
APBI with BT					
Strnad <i>et al.</i> (50)	1,184	16	WBI: 50–50.4 Gy/25–28 fx ± boost	1.0*	27
			APBI: 32 Gy/8 fx or 30.3 Gy/7 fx (HDR) or 50 Gy of 0.60–0.80 Gy/h (PDR)	1.4*	23.3

\*, 5-year event rate; \*\*, skin complications related to RT of G  $\geq$ 3 (P=0.029). fx, fractions; WBI, whole breast irradiation; APBI, accelerated partial breast irradiation; EBRT, external beam radiotherapy; IORT, intraoperative radiotherapy; NR, not reported; HDR, high dose rate; PDR, pulsed dose rate; RT, radiotherapy; BT, brachytherapy.

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