



## Review

# Intraoperative radiotherapy in elderly patients with breast cancer: Is there a clinical applicability? Review of the current evidence



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## ABSTRACT

**Introduction:** Screening and adjuvant postoperative therapies have increased survival amongst women with breast cancer, but these tools are seldom applied in elderly patients. Higher rates of local recurrence occur in those elderly patients who avoid radiotherapy. TARGIT-A and ELIOT trials has been reported to not to be inferior to external beam RT in suitable subgroups of patients. The TARGIT-Elderly trial has been launched in order to confirm the efficacy of intraoperative radiotherapy (IORT) in a well selected group of elderly patients who are more likely to decline radiation treatment.

**Objectives:** Current evidence of the medical literature on the clinical reliability and applicability of intraoperative radiotherapy amongst older women diagnosed with early breast cancer is after summarized.

**Materials and methods:** Literature databases were searched up to June 2015. Terms used to retrieve articles were 'breast cancer', 'elderly', 'intraoperative radiotherapy', 'IORT' and 'IOERT'.

**Results:** Elderly patients with pT1N0 tumours are regarded to be suitable for IORT according to ASTRO and GEC-ESTRO recommendations, respectively.

**Discussion:** In the light of the medical literature we can assume that patients benefit from postoperative radiation therapy, but we still do not know who can be spared from it. These issues emphasize the urgent need to develop and support clinical trials for this older population of breast cancer patients.

**Conclusions:** Whether radiotherapy is beneficial in elderly still remains a matter of debate. IORT along with BCS in a selected subgroup of patients (>70years, pT1N0 tumours) could represent a valid option for a better local control.

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## 1. Introduction

### 1.1. Rationale

One third of breast cancer cases occurs in patients over the age of 65 years, and in more developed countries this proportion rises

to more than 47% after 70 years according to the updated Surveillance, Epidemiology, and End Results (SEER) database [1,2]. Screening and adjuvant postoperative therapies have increased survival amongst women with breast cancer, but these tools are seldom applied in elderly patients. As a matter of the fact it has been shown that the use of radiotherapy decreases with age at diagnosis [3]. In women aged 70 and over, those with screen-detected breast cancers had a higher proportion of breast conserving surgery (71%). Despite this, elderly patients with invasive breast cancer treated with breast conserving surgery (BCS) are often spared from 3 to 5 weeks post-operative radiotherapy (RT), even though RT has been shown to reduce recurrences and increase survival [4–7]. Athas [8] and colleagues suggested that up to 30 per cent of patients who undergo BCS for early breast cancer do not receive postoperative breast irradiation because they live far away

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from radiotherapy centres, or have significant co-morbidities or serious difficulties preventing them from attending daily treatment, especially the elderly. Because of this, elderly patients often decline RT or even opt for mastectomy to avoid radiation treatment [9–12].

Several studies have demonstrated in the past that complete omission of radiotherapy failed in terms of local tumour control, since by adding postoperative external beam radiation treatment (EBRT) the rate of local relapse was reduced to 1% after 5 years. This effect was also seen in elderly patients with small tumors. Hughes et al. [13], observed low local relapse rates of 4% for patients treated with endocrine therapy only after BCS vs. 1% for patients with additional EBRT after 4 years, evaluating a low-risk group of patients with tumors <2 cm and >70 years of age.

## 2. Objectives

We aimed to search in the medical literature for all trials that evaluated the impact of radiation treatment along with BCS in elderly breast cancer and in the light of this to discuss whether there is a clinical applicability of IORT in elderly breast cancer in daily practice. Current evidence of the literature on reliability of intraoperative radiotherapy amongst older women diagnosed with early breast cancer is after summarized.

## 3. Materials and methods

The literature databases MEDLINE, PubMed, the Cochrane Library Controlled Trials Register and Embase, and the National Institutes of Health ClinicalTrials.gov database, were searched up to June 2015. Specific search terms used to retrieve articles were 'breast cancer', 'elderly', 'intraoperative radiotherapy', 'IORT' and 'IOERT'. Only trials investigating breast cancer treatment through breast conserving surgery were selected. Cohort studies were excluded.

## 4. Results

Few trials are specifically focused on radiation treatment after BCS in breast cancer amongst elderly women. 6 of them have been selected for this review. 5 of them were randomised. Milan National Cancer Institute trial was not randomised, but has been selected because of the population size and the long follow up.

### 4.1. CALGB 9343 trial

The CALGB 9343 phase III trial randomised 636 women with invasive breast cancer. This trial started in July 1994 and finished recruiting in February 1999. CALGB 9343 aimed to determine whether there is a benefit to adjuvant radiation therapy after breast-conserving surgery and tamoxifen in women age  $\geq 70$  years (55% > 75 years) who had clinical stage I (T1N0M0) ER positive breast cancer. It showed an absolute decrease in local recurrence rate of 3% (1% versus 4%) at a median follow-up of 5 years and of 7% (2% versus 9%) at a median follow-up of 10.5 years in the RT group. At 10 years, 98% of patients receiving TamRT (95% CI, 96%–99%) compared with 90% of those receiving Tam (95% CI, 85%–93%) were free from local and regional recurrences. There were no significant differences in time to mastectomy, time to distant metastasis, breast cancer-specific survival, or overall survival (OS) between the two groups. Ten-year OS was 67% (95% CI, 62%–72%) and 66% (95% CI, 61%–71%) in the TamRT and Tam groups, respectively [14].

### 4.2. PRIME II trial

The PRIME (Post-operative Radiotherapy In Minimum-risk Elderly) II trial is a multi-centre randomised controlled clinical trial to assess the role of EBRT on local recurrence and survival in low risk older, node negative, women treated by breast conserving surgery and adjuvant endocrine therapy [15]. Between April 16, 2003, and Dec 22, 2009, 1326 women aged 65 years or older with early breast cancer ER positive, axillary node-negative, tumours smaller than 3 cm, and clear margins, who had had breast-conserving surgery and were receiving adjuvant endocrine treatment, were recruited into a phase III randomised controlled trial. Eligible patients were randomly assigned to either external beam radiotherapy or no radiotherapy. The trial is registered on [ISRCTN.com](http://ISRCTN.com), number ISRCTN95889329. Local recurrence was 1.3% (95% CI 0.2–2.3) in women assigned to RT and 4.1% (2.4–5.7) in those assigned no RT ( $p = 0.0002$ ). The HR for local recurrence in women assigned to no radiotherapy was 5.19 (95% CI 1.99–13.52;  $p = 0.0007$ ). 5-year overall survival was 93.9% (95% CI 91.8–96.0) in both groups ( $p = 0.34$ ).

### 4.3. Milan National Cancer Institute non-randomised trial

The Milan National Cancer Institute ran out a prospective non-randomised trial between 1987 and 1992 on 627 elderly cN0 who underwent BCS with or without radiotherapy. 15-year results showed that for pT1 patients LR, distant metastasis and breast cancer death are indistinguishable in the RT and no RT groups in the elderly (LR was 8.1% in both arms, whilst breast cancer death was 11.6% in the RT arm and 10.5% in the no RT arm). For pT2 patients the LR was much higher in those not given RT (14.6% vs 0.8%  $p = 0.004$ ), whilst mortality and distant metastasis did not differ significantly between the two groups (20.2% with RT and 22.5% with no RT) [16]. The effect of EBRT on LR was found to differ significantly ( $p = 0.009$ ) between pT1 and pT2 tumours and EBRT was found to be significantly protective against LR in pT2 disease (HR 0.05  $p = 0.004$ ), but had no effect on pT1 tumours (HR = 0.90  $p = 0.806$ ).

### 4.4. TARGIT-A and ELIOT trials

Two large randomised controlled trials of intraoperative radiotherapy in breast-conserving surgery (TARGIT-A [17] and ELIOT [18]) have been published 14 years after their launch. They both aimed to evaluate the non-inferiority of intraoperative radiotherapy to the conventional 3–5 weeks of whole breast radiation therapy. They used two different techniques and devices to deliver RT. Investigators from the TARGIT-A (ClinicalTrials.gov identifier: NCT00983684) used low energy X-rays 50 kV emitted by Intra-beam<sup>®</sup> system (Carl Zeiss, Oberkochen, Germany) to deliver 20 Gy in a single dose to the applicator surface, which corresponds to 5–7 Gy at 1 cm from the applicator. ELIOT trialists (ClinicalTrials.gov identifier: NCT01849133) employed two mobile linear accelerators capable of delivering 21 Gy electron beam radiation therapy at a single stage, namely the Liac<sup>®</sup> (Sordina, Padua, Italy) and the Novac7<sup>®</sup> (Hitesys, Aprilia, Italy). The in-breast local recurrence rate (LRR) in the IORT arm met the pre-specified non-inferiority margins in both trials and was 3.3% in TARGIT-A compared to 1.3% in the EBRT arm ( $p = 0.042$ ) and 4.4% in the ELIOT trial compared to the 0.4% in the EBRT arm. Looking at subgroup populations, only 10% of the ELIOT population was elderly. The total number of LR events in the ELIOT arm was 35 and only 4 patients out of 62 over 70s developed LR at 5 years ( $p = 0.11$ ). Median follow-up was 2.4 years for the TARGIT-A trial and 5.8 years for the ELIOT trial, hence longer follow up is awaited.

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