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Comparison of mammographic findings after intraoperative radiotherapy or external beam whole breast radiotherapy

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Abstract

Background: The TARGIT (TARGeted Intraoperative Radiotherapy) trial was designed to compare local recurrence and complication rates in breast cancer patients, prospectively randomised to either EBRT (external beam whole breast radiotherapy) or a single dose of IORT (intraoperative radiotherapy). The aim of our study was to compare follow-up mammographic findings, ultrasound and biopsy rates in each group.

Methods: Follow-up imaging and breast biopsies of women from one centre participating in the TARGIT-A trial were independently reviewed by two radiologists blinded to the radiotherapy treatment received.

Results: The cohort consisted of 141 patients (EBRT $n = 80$/IORT $n = 61$). There was no significant difference in the patient or disease characteristics of the two groups. The number of follow-up mammograms and length of follow-up was similar (EBRT/IORT $n = 2.0/2.4$; 4.3yr/5.1yr; $p = 0.386$ χ^2 test). There were no significant differences in mammographic scar or calcification appearances of the post-operative site. Generalised increase in breast density and skin thickening were more common in the EBRT compared to the IORT group ($p = 0.002$; $p = 0.030$, χ^2 test respectively). A trend towards additional ultrasound at follow-up was observed in the IORT group (15 of 61 [24.6%] versus 11 of 80 [13.8%]), however this was not statistically significant ($p = 0.100$ χ^2 test). No disease recurrence was demonstrated on any of the breast biopsies taken. Only one biopsy was reported as fat necrosis in the IORT group.

Conclusions: Mammographic changes were more common following EBRT, although more additional follow-up ultrasounds were performed in the IORT group. IORT is not detrimental to subsequent radiological follow up.

Keywords: TARGIT-A trial; Early breast cancer; IORT; EBRT

Introduction

Current recommended treatment for early stage invasive breast cancer includes breast conserving surgery followed by whole breast radiotherapy.[1] The most common adjuvant whole breast radiotherapy regimen involves delivery of 2.0 Gray (Gy) fractions per session via an external beam over a period of 5 weeks (sometimes followed by a boost to the tumour bed). More recently, the START trials confirmed that a three-week, 15-fraction schedule is at least as safe and effective as standard five-week schedules of adjuvant radiotherapy in women with early breast cancer.[2,3]

The prospect of replacing external beam radiotherapy by equally effective single dose intra-operative tumour bed radiotherapy is an attractive option to dramatically shorten adjuvant radiotherapy treatment time and to avoid the necessity for daily travel, often some distance, especially for old and frail patients and those living in remote areas. Targeted intra-operative radiotherapy (Targit) was initially described as a new innovative radiotherapy technique in 2001.[4] In the TARGIT-A trial, a recent prospective randomised multicentre controlled study of small, good prognosis breast cancer, conventional whole breast radiotherapy was compared to a single dose of 20 Gy delivered to the tumour bed either

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intraoperatively at the time of breast conserving surgical resection or subsequently with conventional external beam radiotherapy. A first analysis at 4 years showed comparable local recurrence rates in the two arms (1.2% vs 0.95%, $p = 0.41$). Furthermore complications associated with radiotherapy were similar in both patient groups.[5] Latest results, presented at the San Antonio Breast Cancer Symposium 2012, showed a 2.0% increase in local recurrence in the IORT group ($p = 0.042$).[6] No significant difference was seen in disease specific survival. Interestingly, fewer deaths, non-breast cancer related, were recorded in IORT group. 5-year risk for death from causes other than breast cancer was lower with TARGIT than with EBRT (17 vs.35, HR 0.47 (0.26–0.84)) and a trend towards improved overall survival was observed in the IORT group (HR 0.70 (0.46–1.07)).[6] Mammographic findings such as distortion, spiculated masses, skin thickening, calcifications and increased density are commonly observed in patients who receive breast radiotherapy. Clinical findings at follow-up or appearances at mammographic follow up often lead to requests for ultrasound of the ipsilateral breast with image guided biopsy if necessary.

However, few studies have compared the mammographic findings and rates of ultrasound examination and biopsy at follow-up in women who have had intraoperative radiotherapy, with those who have received intact breast irradiation. Only limited conclusions can be drawn from the published studies, which contain small numbers of patients, short follow-up and many of which include women who have had both intra-operative radiotherapy and external beam treatment.[7,8]

Additionally, a number of these studies were not randomised but observational studies where the tumour characteristics between the two groups were not matched and so could have led to biased findings.[9,10]

The aim of this study was to compare the mammographic findings and rates of ultrasound examination and biopsy of the ipsilateral breast at follow-up in a large cohort of women who received either intraoperative radiotherapy or whole breast irradiation from within a randomised trial, so ensuring similar patient and tumour characteristics.

Methods

141 patients in total were included in the study. All patients were diagnosed with operable invasive breast carcinoma between 2002 and 2008 in Tayside, Scotland. These patients received wide local excision followed by standard adjuvant systemic drug treatment according to protocols at the time of diagnosis. Radiotherapy was delivered after informed consent and randomisation within the TARGIT trial, which had ethical committee approval. All trial participants were followed up annually with annual clinical examination and 18–24 monthly bilateral 2 view mammography.

Patients were only included in this retrospective analysis when all clinico-pathological data and full follow-up data were available.

Follow-up mammograms of women who received IORT ($n = 61$) were compared with those of women who received EBRT ($n = 80$). A further 11 women who received both treatment modalities were excluded from this study. All mammograms were assessed by two radiologists blinded to the patients' treatment protocol and differences in opinion were resolved by consensus. The focal mammographic appearance of the scar was classified as normal, asymmetry, minor distortion, obvious distortion or spiculated mass. If calcifications were present on the follow-up mammograms these were classified as benign, indeterminate or suspicious. The presence of generalised skin thickening and increased density was documented. The date in relation to time from treatment at which these findings were most conspicuous was recorded and the density of the contralateral breast was assessed using the BI-RADS classification. In addition, the performance, indication and date of ultrasound and/or tissue biopsy of the ipsilateral breast at follow-up was recorded, as were the results of these studies. Significance of differences between the groups was assessed using the Pearson chi square test and p values ≤ 0.05 were taken to indicate statistical significance.

Results

Clinico-pathological details

The median age of the study group was 65 years (IQR 58–70 years), median size of the invasive cancer was 14 mm (IQR 9–18 mm) and 15% of the patients were axillary lymph node positive. There was no significant difference between both groups with respect to patient and tumour characteristics, nor in baseline breast density (Table 1). No disease recurrence or breast cancer deaths occurred during follow-up.

Mammographic findings

In total 332 postoperative mammograms were reviewed. 80% of the cohort had 2–4 follow up mammograms. The number of follow-up mammograms and length of follow-up was similar in both groups (2.0 EBRT versus 2.4 IORT; 4.3 years post EBRT versus 5.1 years post IORT, $p = 0.386$).

There were no significant differences in the mammographic scar and calcification appearances of the post-operative site between the two groups (Table 2). However, increased ipsilateral breast density and generalised skin thickening were more common in the EBRT group compared to the IORT group (25 of 80 [31.3%] versus 6 of 61 [9.8%; $p = 0.002$] and 26 of 80 [32.5%] versus 10 of 61 [16.4%]; $p = 0.030$ χ^2 test) (Fig. 1).

The median time between surgical resection and mature scar appearance was 3.5 years in the EBRT group compared to 3.3 years in the IORT group ($p = 0.276$ χ^2 test).