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Original article

Persistent pain after targeted intraoperative radiotherapy (TARGIT) or external breast radiotherapy for breast cancer: A randomized trial

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ABSTRACT

Persistent pain after breast cancer treatment (PPBCT) affects between 25 and 60% of patients depending on surgical and adjuvant treatment. External breast radiotherapy (EBRT) has been shown to be a risk-factor for PPBCT, raising the question whether intraoperative radiation therapy (IORT), with its smaller radiation field may reduce the development of PPBCT. Using data from the TARGIT-A trial, the aim of this study was to compare these two treatments with regard to development of PPBCT.

A total of 281 patients enrolled in the TARGIT-A trial from the Copenhagen University Hospitals was screened for participation, and a total of 244 patients were included and received a detailed questionnaire. The response rate was 98%, leaving 238 patients for the final analysis.

Pain prevalence were 33.9% in the EBRT group and 24.6% in the IORT group ($p = 0.11$). Treatment with IORT may not alter the risk of PPBCT.

Introduction

Persistent pain following breast cancer treatment affects 25–60% of patients depending on treatment,[1] reflecting a complex pathophysiology involving several pre-, intra- and postoperative risk factors.[2] A recent review of the literature as well as a large nationwide study on persistent pain after breast cancer treatment (PPBCT) showed radiotherapy as a probable risk factor.[1,3] Intraoperative radiation therapy (IORT) has been introduced in clinical trials due to the observation that local recurrence mostly occurs in the area adjacent to the primary tumor.[4] The randomized trial TARGeted Intraoperative radioTherapy TARGIT-A,[5] and a study on intraoperative radiotherapy with electrons (ELIOT)[6] suggest intraoperative radiation therapy is similar to conventional external breast radiotherapy (EBRT) in terms of occurrence of local recurrence. IORT provides a potential for major reduction in patient effort as well as health care resource utilisation, however evaluation of toxicity in the TARGIT-A study[5] did not allow conditions for assessment regarding PPBCT. Furthermore, IORT represents an interesting model to test the influence of radiotherapy on the development of PPBCT, as IORT limits the radiation field and thus the exposure of radiation towards nerves. The purpose of this study was therefore to investigate in detail the development of PPBCT in patients from the Copenhagen University Hospitals, participating in the TARGIT-A study, randomized to treatment with IORT or EBRT. The primary aim of this study was to evaluate prevalence, intensity and frequency of PPBCT to enlighten this safety issue of the TARGIT treatment.

Methods

Trial design

The study was a retrospective questionnaire study based on patients enrolled in the TARGIT-A trial from the Copenhagen University Hospitals. TARGIT-A was a non-inferiority randomized trial registered with clinicaltrials.gov, number NCT0098384. Further description is presented elsewhere.[5]

Patients

Patients identified in the local TARGIT database from March 2007 to January 2010 were examined for eligibility. Inclusion criteria were: Postmenopausal women with primary unifocal and unilateral breast cancer age 50 years or older, T1, N0(N0(i+) and N1(mi)), M0, estrogen receptor positive confirmed by cytological or

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histological examination, suitable for breast conserving surgery, and available for regular follow-up for at least ten years. Exclusion criteria: bilateral breast cancer at the time of diagnosis, previous cancer in and/or irradiation to ipsilateral breast, patients known to have BRCA2 gene mutation, lobular cancer or extensive intraductal component (EIC=>25% of the tumor is intraductal), patients undergoing primary medical treatments (hormones or chemotherapy). In addition patients with previous contralateral breast surgery, local recurrence, metastatic disease, other cancer or axillary lymph node dissection were excluded to rule out influence on pain measurement (see Fig. 1).

Randomisation was made by the TARGIT trial centre in London, UK. Patients were not blinded to treatment. In the present study, data provided from the local TARGIT database, was blinded for the investigators. Data collection and analysis was made at Rigshospitalet, Copenhagen, Denmark. The study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee H-1-2010-029, the Danish Data Protection Agency.

Interventions

Detailed description is presented elsewhere.[5]

Outcomes

The primary outcome was pain present in the area of the operated breast, side of chest, axilla or arm. Secondary outcomes were: intensity and frequency of pain, pain in more than one area, use of analgesics, sensory disturbances and pain elsewhere. A detailed study questionnaire developed for a previous nationwide study of persistent pain and sensory disturbances was used.[1] Questions addressing prevalence for pain was dichotomous yes or no questions. Patients were then asked systematically to specify pain according to location (breast, side of chest wall, axilla or arm), and the intensity on a 0-10 numeric rating scale (0 = no pain, 10 = worst imaginable pain). Frequency of pain was assessed by a 3 point verbal categorial scale: 1) every day or almost every day, 2) one to three days a week or 3) more rarely. Treatment data was provided from the Danish Breast Cancer Cooperative Group (DBCG) and the TARGIT database.

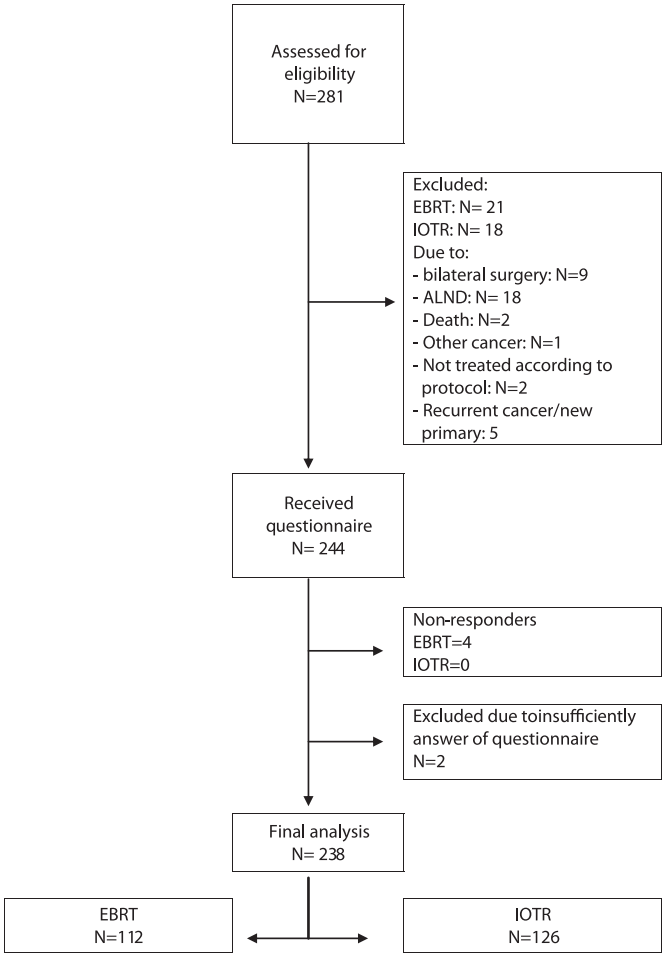

Fig. 1. Flowchart presenting inclusion in the treatment groups.

Sample size

A power analysis was performed on basis of a prevalence of pain of 40% in the treatment group found in the nationwide questionnaire study,[1] corresponding to the same treatment group as this study. We calculated a decrease in prevalence of 15%. Thus, with 80% power and $\alpha = 0{,}05$ a sample size of 120 in both groups were required.

Statistics

Statistical analysis was performed using PASW SPSS 18.0 for Windows (IBM SPSS, Chicago, IL). Normal distributed data was analyzed using the independent *t*-test, binary data using χ^2 or Fischer Exact test, NRS values were analyzed using Whitney–Mann *U*-test. All values were expressed as number of patients, percentages, means ± SD, medians (IQR), OR (95% CI). A *p*-value of 0,05 were considered statistically significant.

Results

Eligible patients were screened from the local TARGIT database and patients ineligible were discarded according to exclusion criteria on basis of registrations in the DBCG database (Fig. 1). Questionnaires were sent out the 16th of April 2010 to eligible 244 patients. Patients not responding one month after received a reminder. The response rate was 98% ($N = 240$). Two questionnaires were discarded due to incompleteness (see Fig. 1). There were no statistically significant differences in age, follow-up, disease characteristics or endocrine therapy (see Table 1). All patients were treated with BCS and sentinel lymph node biopsy. No patients received axilliary lymph node dissection or chemotherapy.

Pain

The prevalence of pain was 33.9% in the EBRT group and 24.6% in the IORT group ($p = 0.11$). Pain localization was similar in the two groups. Pain intensity was for most patients low and not different between the two groups, 71% of the pain patients the EBRT group and 77% in the IORT group scoring 3 or lower on the numerical rating scale. 86.8% of patients reporting pain in the EBRT group reported to have pain on a weekly basis or more often, versus 64.5% of the IORT patients ($p = 0.044$). The prevalence of pain elsewhere (outside the treatment area) were found to be larger in the IORT group than in the EBRT group (40.7% vs. 26.4%) ($p = 0.027$). Prevalence of sensory disturbances was similar (see Table 2).

Discussion

The results of this randomized study suggest that treatment with IORT does not modify the risk of development of PPBCT compared to EBRT. In the EBRT group 33.9% of the patients reported persistent pain in the breast area, side of chest, axilla or arm, whereas in the IORT group, 24.6% reported pain in these areas ($P = 0.11$). The OR for