Aesthetic outcome after breast conserving surgery and either intraoperative radiotherapy or whole breast external beam radiotherapy for early breast cancer: Objective assessment of patients in a randomized controlled trial in Lublin, Poland.

N. R. Williams[1], A. Kurylcio[2], M. Jankiewicz[2], J. Romanek[2], W. Polkowski[2], N. V. Michalopoulos[3], and M. R. Keshtgar[3]

[1]Surgical & Interventional Trials Unit, Division of Surgery and Interventional Science, UCL, London, United Kingdom

[2]Medical University of Lublin, Lublin, Poland

[3]Royal Free London NHS Foundation Trust, London, United Kingdom

Correspondence should be addressed to Norman Williams (norman.williams@ucl.ac.uk)

Abstract

The international randomized controlled TARGIT A (TARGeted Intraoperative radiotherapy) trial demonstrated non-inferiority between the technique of TARGIT (Intra-Operative RadioTherapy (IORT) with Intrabeam®) and whole-breast external beam radiotherapy (EBRT) as part of the treatment for women with early breast cancer. The aim of this sub-study was to see if the single high dose of IORT leads to impaired aesthetic outcome in a group of patients participating in the trial at a single site.

Frontal digital photographs were taken of women and analyzed, blinded to treatment received, by BCCT.core software. This produced scores for various measures of color.

29 women (16 EBRT, 13 IORT) between 49 to 79 years old had photographs taken at baseline (up to 2 days prior to surgery), and again at 12 months (median 364 days). At 12 months there was a significant difference in cEMDL (p=0.002, Wilcoxon Two-Sample test, 2-sided) and other measures, indicating more “redness” in the breasts of the women in the EBRT group compared with the IORT group. This difference persisted after adjusting for tumor size, body mass index and age (p=0.0198, multiple regression analysis).

This study provides further evidence for the early beneficial effect of TARGIT on aesthetic outcome.

Keywords

TARGIT, intraoperative, IORT, early breast cancer, aesthetic outcome, radiation therapy.

Short Title

Aesthetic outcome after breast conserving surgery and intraoperative radiotherapy.

Introduction

The surgical treatment of early breast cancer has moved from radical (mastectomy) to minimally invasive (breast conserving surgery), and the benefits of this approach are well established [1,2].

However, radiotherapy treatment continues to involve irradiation of the whole breast. Techniques of intra-operative radiotherapy (IORT) deliver therapeutic irradiation to the tumor bed from within the breast after wide local excision. Data from the randomized controlled trial of targeted intraoperative radiotherapy (TARGIT) has confirmed that, in selected women with early breast cancer, the technique is safe and as effective as conventional external beam radiotherapy to the whole breast [3,4,5,6].

Furthermore, improvements in survival of patients with breast cancer [7] mean that the aesthetic outcome has become an increasingly important consideration. External beam radiotherapy can cause significant differences in color such as erythema, hyperpigmentation of the breast, hypopigmentation of the nipple–areola complex and telangiectasia [8], and radiotherapy-associated fibrosis can impact on symmetry by causing upward retraction of the inferior mammary sulcus and/or the nipple–areola complex [9].

A variety of methods for determining aesthetic outcome have been developed, many based on the subjective, overall cosmetic score classifying outcome as excellent, good, fair and poor as described in 1979 by Harris et al. [10]. Cardoso et al. [11,12] developed a software program based on this classification system. Breast Cancer Conservative Treatment cosmetic results (BCCT.core) combines objective measures of asymmetry, skin color and scar from digital photographs, resulting in an overall aesthetic score that is a reproducible, objective evaluation of breast cancer conservation treatment [13].

The aim of this study was to compare the aesthetic results of a single biologically effective dose of radiotherapy given using TARGIT, with standard whole breast external beam radiotherapy, and expands on work presented previously [14].

Materials and Methods

Women from a single site (Medical University in Lublin, Poland) participating in the TARGIT trial were included in this study. Patients were randomized to receive either IORT by the Intrabeam® (Carl Zeiss, Germany) device or conventional external beam radiotherapy as per local protocol.

IORT was given according to the TARGIT technique as described [3]. Briefly, an applicator of appropriate size was placed directly into the lumpectomy cavity and the entire dose of radiation therapy was delivered to the tumor bed in a single fraction at the time of surgery (20Gy at surface of the applicator equivalent to 5–6 Gy at depth of 1 cm from surface of the applicator). Therefore radiotherapy was given to the tumor bed, while sparing the normal tissue away from the tumor from the effects of radiation.

EBRT was given to the whole breast as 25 fractions of 2Gy each, plus 5 fractions of 2Gy each, for a total dose of 50Gy plus 10Gy boost to the tumor bed.

This study was conducted in accordance with the Declaration of Helsinki (1964), and local Ethical Committee approvals were in place before commencement. Written informed consent was obtained by all patients prior to enrolment, after which digital photographs were taken at baseline (prior to surgery) and one year later. Frontal views of the unclothed torso (from neck to navel) were used for objective analysis by BCCT.core software (BCCT.core 2.0, INESC Porto, Portugal). To extract color features of each breast, a histogram

analysis was carried out followed by an evaluation of dissimilarity [11]. All photographs were processed by one operator (NM) blinded to treatment received.

Data on tumor and patient characteristics, and treatments given, were obtained from hospital notes.

SAS version 9.4 was used to calculate the summary statistics of the population, the comparison of treatment groups using the 2-sided Wilcoxon Two-Sample test, and multiple regression analysis.

Results

42 patients from this site were randomized into the TARGIT A Trial. Of these, 37 women gave consent to participate in this sub-study. Eight patients were excluded from analysis as they either (a) did not have a photograph taken at one year (six patients), or (b) received both IORT and EBRT (two patients). The study population therefore comprised 29 women (16 EBRT, 13 IORT; see Figure 1), median age 56 years (range 49 to 79) who had photographs taken at baseline (up to 2 days prior to surgery), and again at 12 months (median 364 days). Patients' demographics, tumor characteristics and adjuvant treatments are summarized in Table 1.

For patients who received IORT, the most commonly used applicator sizes were 45 and 40mm (four patients each), followed by 35mm (three patients), 30 and 25mm (one patient each). Within the TARGIT A Trial, IORT could be given either pre-pathology (at the same time as the wide local excision) or post-pathology (in a subsequent procedure after histopathology review of the excised tumor) [4]. All patients in this study were in the pre-pathology cohort.

All patients randomized to receive external beam radiotherapy had a complete course of treatment, with no gaps. Note that two patients were excluded from analysis as they had IORT followed by EBRT (without boost), which is part of the "risk adjusted" strategy of the TARGIT technique [6].

At 12 months there were significant differences in several of the measures of color (see Figure 2), indicating more "redness" in the treated breasts of the women in the EBRT group compared with the IORT group. This difference remained after adjusting for tumor size, body mass index and age (p=0.0198). There were no significant differences in overall classification or measures of symmetry between treatment groups.

Discussion

This objective evaluation complements our previous work [15] and indicates that aesthetic outcome one year after surgery in patients treated with IORT when given as a first procedure (pre-pathology) is significantly better than those treated with EBRT.

A likely explanation for this finding is that as intraoperative radiotherapy is delivered from within the breast the negative effect of radiotherapy to the skin is minimized. This result is in line with findings of the TARGIT trial showing that radiation toxicity was more frequent in the EBRT group than in the TARGIT group [3].

An argument can be made that the color changes associated with EBRT are of little consequence to the patient [16]. However, another view is that the "redness" is a surrogate for effects of radiation on normal tissue, and there may be unseen yet potentially serious side effects on the lungs and heart using EBRT that are not found with IORT [17]. For example, it has been shown that compared to the entire dose of radiation

delivered by TARGIT, just one fraction of EBRT is associated with a significantly greater change in γ-H2AX foci number in peripheral blood lymphocytes (a marker of dose delivered to the heart and great vessels) [18].

Conclusions

This objective assessment of aesthetic outcome in patients from a randomized trial demonstrates that "redness" is significantly greater after one year in patients receiving EBRT compared with those receiving IORT, and adds to the evidence of the beneficial outcomes of TARGIT.

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Conflict of Interest

The manufacturer of the Intrabeam instrument (Carl Zeiss Meditec) pays for travel, accommodation, and other expenses to attend meetings where TARGIT-related presentations are made.

Ethical Approval

This sub-study was conducted in accordance with the Declaration of Helsinki (1964), and local Ethical Committee approvals were in place before commencement. Written informed consent was obtained by all patients prior to enrolment.

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