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Original article

Predictors for poor cosmetic outcome in patients with early stage breast cancer treated with breast conserving therapy: Results of the Young boost trial

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ABSTRACT

Purpose: In the Young Boost trial (YBT), breast cancer patients ≤50 years of age, treated with breast conserving therapy (BCT) were randomized between a 26 Gy boost dose and a 16 Gy boost dose, with local recurrence as primary and cosmetic outcome (CO) as secondary endpoint. Data of the YBT was used to investigate which factors are related with worse cosmetic outcome after BCT.

Methods: From 2004 to 2011, 2421 cT1-2N0-2a breast cancer patients were randomized. CO was scored subjectively by the patient and physician, and objectively using BCCT.core: at baseline, one and four years after treatment. Associations between potential risk factors for worse cosmetic outcome, based on the objective BCCT.core, were investigated using a proportional odds model.

Results: At four years, CO was significantly better in the standard boost group for all three scoring methods (satisfied CO ±65% vs 55%). A photon boost, high boost dose, poor cosmesis before radiation therapy, large boost volume and adjuvant chemotherapy significantly deteriorated CO.

Conclusion: Important risk factors for worse CO were the use of a photon boost instead of an electron boost, a high boost dose, cosmesis at baseline, adjuvant chemotherapy and boost volume. These results can be used to define strategies aimed at improving CO.

In women with early breast cancer treated with breast-conserving surgery (BCS), whole breast radiation therapy (RT) reduces the risk of local recurrence at 5 years from 26% to 7% [1]. The EORTC "boost versus no boost" trial showed that an additional boost of 16 Gy to the tumour bed reduces the risk for local failure by a factor of 2, with an increased incidence of moderate/severe fibrosis as negative side effect [2]. However, after 10 years of follow-up, the risk of local failure remained unacceptably high, in the younger patients, even after a boost, with a risk of 13.5% in patients ≤40 years, and of 8.7% in patients 41–50 years [3]. Therefore, in 2004, the Young Boost trial (YBT) was launched (NCT00212121) with the primary aim to investigate whether a higher boost dose of 26 Gy to the tumour bed would further reduce local recurrence rate in these young patients with cosmetic outcome as secondary endpoint.

Several risk factors for deterioration of the cosmetic outcome have been described in literature, for example breast size [4,5], tumour size [6,7], excision volume [6,7], tumour location [5–7], post-operative complications [4,5], boost volume [8], a photon boost [7,9], total dose [10] and dose max [8,9,11]. However, no data are available concerning a boost dose as high as 76 Gy EQD2, which makes the YBT unique. Moreover, in order to be able to improve cosmetic outcome, we need to continue to update the knowledge of risk factors for cosmetic outcome with data derived from the most current literature.

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It was decided by the independent data monitoring committee that the primary endpoint (i.e. local failure) should not be analysed yet. However, they recommended that the cosmetic outcome, which was a secondary endpoint, could be analysed by treatment arm now that up to 4 years of follow-up is available. Previously, we reported that the distance from nipple to inframammary fold, the length of the breast contour and the severity of fibrosis were associated with patient reported outcome in the YBT [12]. The primary aim of this paper is to report on the cosmetic outcome in the YBT; the secondary aim is to define risk factors for worse cosmetic outcome in this patient population, based on the objective BCCT.core.

Patients and methods

Patient population and treatment

Patients younger than 51 years with non-metastatic, histological proven invasive breast cancer, pT1-2N0-2a [13] were eligible for the trial when fulfilling the following inclusion criteria: ECOG performance scale $\leq$2; wide local excision (WLE); microscopically complete (no tumour on ink) or focally involved (defined as: "tumour (ductal carcinoma in situ or invasive carcinoma) on ink in an area of less than 4 mm") resection; sentinel lymph node biopsy and/or axillary lymph node dissection; no primary systemic treatment; no previous history of malignant disease, except adequately treated carcinoma in situ of the cervix or basal cell carcinoma of the skin. Exclusion criteria were: residual microcalcifications on mammogram; histological other than invasive adenocarcinoma; in situ carcinoma of the breast without invasive tumour; multicentric tumours and multifocal tumours excised using multiple excisions; bilateral invasive breast cancer and concurrent pregnancy. More information can be found at https://clinicaltrials.gov/show/NCT00212121.

Patients were randomized to receive a standard 16 Gy or a high 26 Gy boost to the tumour bed after 50 Gy whole breast irradiation, given in 2 Gy fractions. Other fractionation schemes, including simultaneous integrated boost (SIB) techniques were allowed as well, as long as the biological equivalent dose (EQD2), calculated with an α/β of 10 for tumour control, was similar. The overall treatment time was kept constant in both randomization arms, i.e. 6.5–7 weeks (see Supplementary file for more extensive information concerning the RT protocol). RT had to start within 10 weeks after surgery. In case adjuvant chemotherapy was given immediately after surgery, RT should start within 6 months after surgery and within 6 weeks after the last cycle of chemotherapy. In case endocrine treatment was planned, this was recommended to start after completion of the RT. Stratification factors were age (<vs> 40 yrs.), pathological tumour size (<vs> 3 cm), oestrogen receptor status, nodal status, interstitial/external boost and institute. Patients were stratified at the time of randomization; treatment was assigned using a minimization technique [14].

The study was centrally approved by the medical ethical committee of the Netherlands Cancer Institute and by the local medical ethics committees. All patients gave their written informed consent to participate.

Recording of fibrosis and cosmetic outcome

Cosmetic outcome and fibrosis were scored at baseline, i.e. after surgery but prior to start of RT, at 1 year, 4, 7 and 10 years of follow-up (FU). Standardized digital photographs were taken at the same time-points.

The presence of fibrosis (whole breast and specifically in the boost area) was scored by the physician on a 4-point scale: none, minor, moderate or severe.

Cosmetic outcome was scored according to the following three scoring systems:

BCCT.core software [15,16]: digital photographs in anterior–posterior view were analysed using the BCCT.core software program. Pre-determined points were designated by the examiner, followed by an automatic calculation of an overall cosmetic score: excellent, good, fair or poor (score 1–4; higher score means worse outcome). This score is based on symmetry, skin colour and scar visibility.

Physician's score. Physicians scored cosmetic outcome using the Harris scale [17]: excellent, good, fair or poor, indicated as score 1–4 respectively.

Patient's questionnaire. Patients' satisfaction with the cosmetic outcome was scored using a validated patient's questionnaire developed by Sneeuw et al. [18]: very satisfied, satisfied, not dissatisfied, dissatisfied or very dissatisfied (score 1–5 respectively).

For the analyses of crude percentages, the scores very satisfied or satisfied and good or excellent were grouped as 'satisfactory'.

Analysis of risk factors for fibrosis and cosmetic outcome

The following risk factors, scored on the Case Report Forms, were investigated:

RT related risk factors: dose to the tumour bed; irradiated boost volume (per 10 cc), defined as the volume receiving more than 95% of the boost dose for external photon irradiation, and within 85% of the boost dose for electron and interstitial irradiation; photon boost versus electron boost; Simultaneous Integrated Boost (SIB) versus sequential boost; energy used for whole breast irradiation (WBI) and the use of CT-scan for planning.

Systemic therapy related factors: adjuvant chemotherapy, adjuvant endocrine therapy.

Surgery related factors: excision volume (per 10 cc); post-operative complications and seroma, scored as yes, no, or unknown. Postoperative complications were defined as the presence of infection and/or haematoma of breast and/or axilla. Oedema was not considered as a complication. Seroma was analysed separately from post-operative complications, as we assumed there might be a correlation with oncoplastic surgery.

Tumour related factors: tumour location (lateral tumour location vs. central and medial/upper tumour location vs. central) (Supplementary figure).

Patient characteristics: age (per year) and cosmetic score at baseline.

Statistical analysis

The percentages of patients with satisfactory cosmetic scores in the high- and standard boost group were compared at baseline, 1 year, and 4 years with Fisher's exact test. Associations between potential risk factors and cosmetic outcome, measured by BCCT.core, were assessed with a proportional odds model, in order to treat the cosmetic outcome as a variable with ordered categories. An important assumption of the proportional odds model is that the association between each pair of outcome groups is the same, so that for example the comparison between a score of 1 (=Excellent) versus a score of 2 (=Good), 3 (=Fair) or 4 (=Poor), and the comparison of 1 or 2 versus 3 or 4 can be modelled by the same parameter. The assumption was verified by calculation of linear predictions from a logit model, used to model the probability that the outcome is greater than or equal to a given value (for each cosmetic outcome level). These were compared between categories of one predictor variable at a time, and no great differences were observed.

Both the number of patients with moderate and severe fibrosis, and of patients with severe fibrosis at baseline, 1 year, and 4 years was calculated as a percentage of the total number of patients with

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