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Three-dimensional conformal hypofractionated simultaneous integrated boost in breast conserving therapy: Results on local control and survival

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ABSTRACT

Purpose: To report on local control and survival after breast conserving therapy (BCT) including three-dimensional conformal simultaneous integrated boost irradiation (3D-CRT-SIB) and on the influence of age on outcome.

Patient and methods: For this study, 752 consecutive female breast cancer patients (stages I–III), treated with 3D-CRT-SIB at the University Medical Center Groningen from 2005 to 2008, were retrospectively identified. Median age was 58.4 (range 26–84) years. The SIB fractionation used was: 28 × 1.8 Gy (whole breast) and 28 × 2.3 Gy or 2.4 Gy (tumour bed). Next to outcome, we estimated the effect of age on the recurrence-free period (RFP) by multivariate Cox regression survival analysis.

Results: Median follow-up was 41 (range 3–65) months. Local control was 99.6% at 3 years (6 ipsilateral recurrences). The 3-year locoregional control, RFP and overall survival (OS) rates were 99.2%, 95.5%, and 97.1%, respectively. In multivariate analysis, tumours >2 cm (hazard ratio (HR) 3.11; 95% confidence interval (CI) 1.57–6.17) and triple negativity (HR 3.03; 95% CI 1.37–6.67) and not age were associated with impaired RFP.

Conclusions: At 3 years, the 3D-CRT-SIB technique in BCT results in excellent local control and OS. Age was not a risk factor for any recurrence.

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Radiotherapy (RT) is considered an integral part of breast conserving therapy (BCT) in patients with invasive breast cancer, since both local control (LC) and overall survival (OS) improved significantly by combining breast conserving surgery with RT [1,2]. Currently, BCT is considered standard of care for patients with stages I–II disease [3].

Conventional breast RT is delivered to the whole breast and is often followed by an additional boost dose to the tumour bed [4]. Breast irradiation with a boost to the tumour bed provides significantly higher LC rates than whole breast irradiation alone, 93.8% vs. 89.8% at 10 years, respectively [5]. Since 2005, at our department, RT after lumpectomy is administered with a three-dimensional conformal-technique with a hypofractionated simultaneous integrated boost (3D-CRT-SIB). With the 3D-CRT-SIB technique [6], whole breast and boost irradiation are combined in one treatment plan and are given simultaneously. With the SIB, the mean volume receiving ⩾107% of the breast dose was reduced by 20%, the mean volume outside the boost PTV receiving ⩾95% of the boost dose was reduced by 54%, and the mean heart and lung dose were reduced by 10% compared to the sequential boost technique [6]. Due to the higher dose per fraction to the tumour bed, the overall treatment time can be reduced with 2 weeks, which adds substantially to patient convenience. In addition, we showed that the 3D-CRT-SIB was superior to the sequential boost-technique with respect to unintended excessive dose to the area outside the boost [6]. Despite the somewhat higher dose per fraction to the boost area, acute toxicity after 3D-CRT-SIB was mild and remained within acceptable limits [6].

Studies reporting on BCT show that treatment outcome in terms of LC is significantly worse in younger patients compared to older patients [7–10]. In the European Organisation for Research and Treatment of Cancer (EORTC) study 22881-10882, the absolute benefit of a boost in terms of local control was most pronounced in young patients [5]. Differences exist between the aforementioned 3D-CRT-SIB technique, and the techniques that were used in the EORTC study 22881-10882. In contrast to the EORTC study, all patients treated with 3D-CRT-SIB were planned using a computer tomography (CT) scan which may improve reconstruction of the exact location and volume of the boost area. Furthermore, CT-based planning provides more accurate information on the dose

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distribution and offers the opportunity to optimise dose homogeneity and dose conformity. As the local recurrence rate is expected to be highest in younger patients, the question arises whether such a difference would also be present after breast irradiation with the 3D-CRT-SIB technique.

Therefore, the purpose of this paper was to evaluate the clinical outcome of a consecutive series of patients with invasive breast cancer treated with the 3D-CRT-SIB as part of BCT and to investigate the influence of age on treatment outcome.

Patients and methods

Study population

The study population was composed of 752 consecutive female invasive breast cancer patients (stages I–III) treated with breast conserving surgery. All patients were treated with postoperative RT using 3D-CRT-SIB at the department of Radiation Oncology of the University Medical Center Groningen between January 2005 and January 2008. Excluded were male patients, patients with a history of invasive cancer (except non-melanoma skin cancer or carcinoma in situ of the cervix), previous irradiation to the thorax, patients diagnosed with synchronous contralateral breast cancer (i.e., breast cancer diagnosed in both breasts simultaneously or within a 3-month period of diagnosis of the first tumour), and patients treated with neo-adjuvant chemotherapy. The median age at diagnosis was 58.4 (range 26–84) years. There were 204 patients (27.1%) aged 50 years or younger at time of diagnosis. Patient, tumour and treatment characteristics are listed in Table 1.

Data collection

Patient, tumour and treatment-related characteristics as well as follow-up data were collected retrospectively from the medical files. The following data were collected: age at diagnosis, information regarding primary surgery, adjuvant chemotherapy and hormonal treatment, regional RT, tumour recurrence, distant metastases, and death. Data regarding tumour size, lymph node status, number of metastatic lymph nodes, positive apical lymph nodes, histologic diagnosis and grade, presence of lymphovascular invasion and extensive ductal carcinoma in situ (DCIS), multifocality, resection margin status, and receptor status were obtained directly from the pathology report. Patients were staged according to the TNM classification system (IUCC 2002) [3]. In 52 cases with missing data (mainly follow-up), the general practitioner was contacted for additional information. In 42 cases (80.8%), the additional follow-up data were provided. Data were entered in a database and maintained by a data manager. Data collection of the present study was conducted under compliance of the hospital institutional review board regulations.

Toxicity scoring

During routine follow-up at our department, the physician-rated, late toxicity was prospectively assessed according to the Common Terminology Criteria of Adverse Events version 3.0 (CTCAE v3.0) [11]. Routine out-patient visits were made yearly, from the first year to 5 years after RT.

Definitions

Because it was not possible to differentiate between a true LR and new primary tumours in the ipsilateral breast, LR was defined as any recurrence, either invasive or in situ carcinoma, in the ipsilateral breast or overlying skin. Regional recurrence (RR) was defined as

Table 1
Patient and tumour characteristics ($n = 752$).

Characteristic	*n*	(%)
Age at diagnosis (y)		
⩽50	204	(27.1)
>50	548	(72.9)
BRCA 1 or 2 mutation		
Absent	22	(2.9)
Present	12	(1.6)
Unknown	718	(95.5)
Pathological T-stage		
T1	561	(74.6)
T ⩾ 2	191	(25.4)
Pathological N-stage		
N0	522	(69.4)
N1	190	(25.3)
N2+	37	(4.9)
Nx	3	(0.4)
Histology		
Invasive ductal	658	(87.4)
Invasive lobular	66	(8.8)
Other	28	(3.7)
Multifocality		
No	728	(96.8)
Yes	24	(3.2)
Status resection margins		
Negative	635	(84.4)
(Focally) positive	109	(14.5)
Missing	8	(1.1)
Differentiation grade		
I/II	550	(73.1)
III	193	(25.7)
Missing	9	(1.2)
Lymphovascular invasion		
Absent	696	(92.6)
Present	56	(7.4)
Extensive DCIS		
Absent	684	(91.0)
Present	68	(9.0)
Extra nodal growth		
Absent	694	(92.3)
Present	58	(7.7)
Oestrogen receptor (ER)		
Positive	595	(79.1)
Negative	126	(16.8)
Missing	31	(4.1)
Progesterone receptor (PR)		
Positive	514	(68.4)
Negative	205	(27.3)
Missing	33	(4.4)
HER2 receptor		
Positive	69	(9.2)
Negative	626	(83.2)
Missing	57	(7.6)
Triple negative[a]		
No	659	(87.6)
Yes	93	(12.4)
Adjuvant chemotherapy		
No	486	(64.6)
Yes	266	(35.4)
Adjuvant hormonal therapy		
No	461	(61.3)
Yes	291	(38.7)
Adjuvant trastuzumab		
No	715	(95.1)
Yes	37	(4.9)
Regional radiotherapy		
No	707	(94.0)
Yes	45	(6.0)

Table 1 (*continued*)

Characteristic	*n*	(%)
Boost dosage		
Low (64.4 Gy)	573	(76.2)
High (67.2 Gy)	179	(23.8)

Abbreviations: DCIS: ductal carcinoma in situ; HER2: human epidermal growth factor receptor 2.

[a] ER negative, PR negative, and HER2 negative.

recurrence in the ipsilateral axillary, supraclavicular or internal mammary lymph nodes without clinical or radiologic evidence of distant metastases. Locoregional recurrence (LRR) was defined as either LR or RR. LRR was considered an event if this was not preceded by distant metastases (i.e., first event). In case of simultaneous LRR and distant metastases, the locoregional event was considered the first event in the analyses.

Distant metastases were defined as all cancers, spread from the primary tumour, occurring at sites other than local or regional sites. Death of disease was defined death preceded by LRR or distant metastases. Overall survival considered deaths of any cause.

Endpoints were calculated as the interval between pathological diagnosis of primary breast cancer and the event of interest or date of last follow-up. As few LRR events were expected, an additional endpoint was defined to investigate disease progression, including the recurrence-free period (RFP) defined as the time of date of diagnosis until any recurrence (LRR or distant metastases). RFP was presented as 1 minus the cumulative incidence of any recurrence.

Multifocality was considered positive as two or more foci of the invasive component were present in the pathological specimen. Resection margins were considered microscopically involved in case of a positive resection margin or a margin of less than 1 mm. Otherwise, the margin was considered to be tumour free. DCIS was classified as extensive if 10 or more ducts were involved. The apical lymph node was defined as the most cranial positioned lymph node in the axillary dissection specimen as marked by the surgeon.

Radiotherapy

Patients were treated with 3D-CRT-SIB as part of BCT. This technique and choice of fractionation has been described in more detail by van der Laan et al. [6]. Briefly, with the SIB technique, breast and boost beams are combined in one integrated treatment plan, i.e., patients are treated with the same plan each fraction throughout the entire course of treatment. Fractionation schemes used were 28 daily fractions of 1.8 Gray (Gy) to the whole breast PTV and 2.3 Gy (76.2%) or 2.4 Gy (23.8%), in case of involved or focally positive resection margins, to the boost planning target volume (PTV), adding up to a total dose of 64.4 Gy or 67.2 Gy. These fractionation schemes are biologically equivalent to the sequential boost-technique comprising 25 fractions of 2 Gy to the whole breast PTV followed by a boost irradiation in 8 or 10 fractions, using an α/β ratio of 10 Gy for tumour response, based on the linear-quadratic cell survival model [12].

The breast clinical target volume (CTV) included the glandular breast tissue of the ipsilateral breast, excluding the major pectoral muscle, the ribs and the skin. The tumour bed CTV was delineated guided by the presence of the surgical clips, hematoma, seroma and/or other surgery-induced changes. Breast and boost CTVs were expanded with a margin of 5 mm to generate the breast and boost PTVs. For the breast PTV, a margin of 10 mm was used in the cranial and caudal directions. The 3D-CRT-SIB treatment plans consisted of tangential breast beams with multileaf collimator (MLC) shielding conformal to the breast PTV. In general, one or more boost beams with a non-tangential beam-direction were added conformal to the boost PTV. Beam weights, wedge fractions and MLC settings for all beams were manually adjusted in such a way that the 95%-isodose closely encompassed the PTVs in 3 dimensions, and volumes receiving $\geqslant$107% of the dose prescribed to the PTVs were minimized. No specific constraints for organs at risk were used. Beam directions, multileaf collimator settings, beam shapes and beam weights were manually optimised to minimise the dose to heart, lung and breast tissue as much as possible without compromising target coverage. Field in field segments were used to improve dose homogeneity and dose-to-target conformity. Attempts were made to cover at least 98% of virtual breast and boost PTVs (original PTVs excluding the build-up region) with 95% of the prescribed dose. All beams were delivered with a linear accelerator using 6 or 15 MV photons.

Regional RT, including the axillary, supra and infraclavicular nodal areas, with or without the internal mammary nodes (IMN), was indicated in case of more than 3 axillary lymph node metastases or in case of a positive apical lymph node (total $n = 45$; 6%). Indications for IMN-RT were medial located tumours with indication for regional RT, pathological positive IMN sentinel node, and positive flow to an IMN lymph node, which was not removed during surgery.

Systemic therapy

Patients with node-positive disease and high risk node-negative tumours were treated with adjuvant systemic therapy according to national guidelines [3]. Risk classification was based on tumour size, grade, hormonal receptor status and age. Chemotherapy consisted of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) in 260 (97.7%) patients. Six patients received a combination of adriamycin and cyclophosphamide (AC). In this series, none of the patients was treated with taxane-based chemotherapy. In general, in node-positive disease, chemotherapy was administered first followed by RT, whereas in node-negative patients, RT was given first. The treatment sequence was based on regional consensus of opinion. Adjuvant hormonal therapy was indicated for all intermediate and high risk hormonal receptor-positive patients. Depending on menopausal status, tamoxifen or aromatase inhibitors were given. For patients receiving chemotherapy, trastuzumab was recommended for all patients with tumours overexpressing the human epidermal growth factor receptor 2 (HER2) [3].

Statistical analysis

Contingency tables were used to present the patient, tumour and treatment-related characteristics, number of first events and second cancers (i.e., malignancy not related to a recurrence or primary tumour). Furthermore, the observed proportions of late toxicities are reported.

The unadjusted 3-year actuarial rates of LC, locoregional control (LRC), RFP, and OS and corresponding 95% confidence intervals (CIs) were calculated using the Kaplan–Meier method. Given the median follow-up duration, we presented the 3-year rates. The dataset was stratified according to age ($\leqslant$50 and >50 years) and outcomes were compared with the log rank test.

Univariate analyses and multivariate analysis were performed using the Cox proportional hazard model to identify prognostic factors for RFP. The covariates that were univariately related to the endpoint ($p < 0.10$) were entered in the multivariate analysis. Adjusted hazard ratios (HRs) and 95% CIs were calculated. In addition to the dichotomized covariate of age at diagnosis ($\leqslant$50 and >50 years), we explored the impact of other age groups in the analysis, by categorizing age in 4 subgroups ($\leqslant$40, 41–50, 51–60 and >60 years). Due to the high correlation between both oestrogen receptor status and triple negativity (i.e., oestrogen receptor (ER)

negative, progesterone receptor (PR) negative, HER2 negative), and lymph node status and regional RT (Pearson's $R > 0.8$), only triple negative receptor status and lymph node status were included in the multivariate analysis.

To explore the impact of competing risks on outcome, two sensitivity analyses were performed. First, all patients who developed a second cancer during follow-up were excluded from the analysis and second, all patients who had a non-breast cancer related death were excluded.

All tests were two-sided and probability values of <0.05 were considered to be statistically significant. The analyses were performed using the SPPS software package, version 16.0 for Windows (SPSS, Chicago, IL, USA).

Results

Patterns of failure

Median follow-up was 41 (range 3–65) months. The patterns of failure are listed in Table 2. During follow-up, 6 patients developed an ipsilateral LR with a median time to LR of 33.5 (range 13–61) months, including 4 invasive tumours and 2 pure DCIS. Five out of these recurrences were in-breast recurrences and were treated with salvage mastectomy. So far, these 5 patients remained disease-free. After 14 months of follow-up, 1 out of these 6 patients developed lymphangitis carcinomatosa in the treated breast with concurrent supraclavicular and distant metastases. She was treated with palliative chemotherapy, but died within 2 years.

In the 2 patients with a pure DCIS LR, these were located outside the boost fields. In 2 other patients with an invasive LR, the LRs were localized just beneath the scar of the primary lumpectomy and within the boost PTV. The fifth invasive LR was seen in a patient with a multifocal primary tumour with extensive DCIS. The LR was present diffusely through the whole breast, with massive lymphangioinvasion.

In total, 5 patients developed an isolated RR. In 2 patients, this RR was localized in the axilla, in 1 patient in the supraclavicular region, in 1 patient in the IMN and in 1 patient in both supraclavicular and IMN simultaneously. None of these patients had been treated with regional RT and all RRs were located outside the primary radiation fields. Supraclavicular recurrences with concurrent distant metastases were observed in 2 patients. One of these 2 patients died of disease. During follow-up, 3 patients with a RR had disease progression with distant metastases. Two of these patients eventually died.

Distant metastases as first event developed in 27 patients, of whom 11 (40.7%) subsequently died. In total, 15 patients died of disease progression.

Eleven patients died of other causes, including cerebrovascular events ($n = 2$), liver cirrhosis ($n = 1$), suicide ($n = 1$), secondary malignancies ($n = 5$) and unknown causes ($n = 2$), respectively.

Table 2
Patterns of failure ($n = 752$).

First event	*n*	(%)
Local recurrence (LR)[a]	6	(0.8)
Regional recurrence (RR)[b]	8	(1.1)
Distant metastases (DM)	27	(3.6)
Death of disease	15	(2.0)
Death of all causes	26	(3.5)
Secondary malignancy		
Contralateral breast cancer	11	(1.5)
Ovarian cancer	1	(0.1)
Other	16	(2.1)

Median time since diagnosis (mos) (range) 41 (3–65).
[a] One patient developed LR, RR and DM simultaneously.
[b] Two patients developed RR and DM simultaneously.

Primary outcomes

The 3-year LC was 99.6% (95% CI 99.5–99.6), RFP 95.5% (95% CI 95.4–95.5), and OS 97.1% (95% CI 97.0–97.1), respectively. In Figs. 1 and 2, the Kaplan–Meier curves of LC and OS are shown. The actuarial 3-year rates, comparing young and old patients ($\leqslant$50 and >50 years at diagnosis) including the 95% CIs of all endpoints and the corresponding *p*-values of the log-rank test are listed in Table 3. No significant differences in clinical outcome were found according to age.

Secondary malignancies

Secondary malignancies developed in 28 patients (3.7%). In 11 cases, the secondary primary tumour was located in the contralateral breast. One patient (3.6%) developed oesophageal cancer; 7 other patients (25.0%) developed cancer elsewhere in the gastrointestinal tract; 3 patients (10.7%) lung cancer; 2 patients (7.1%) head and neck cancer; 2 patients acute myeloid leukemia; 1 patient ovarian cancer and 1 patient endometrial carcinoma. Five patients, who developed a second malignancy other than contralateral located breast cancer, died of this second cancer.

Late toxicity

Toxicity scores were available in 612 patients (81.4%). The proportion of patients with grade 2 or higher fibrosis in the breast (i.e., fibrosis in the boost area and/or non-boost area) ($n = 49$), grade $\geqslant 2$ telangiectasia in the treated breast ($n = 19$), breast oedema ($n = 63$), any pain to the thoracic wall ($n = 42$), and rib fractures ($n = 2$) were observed in 9.1%, 3.2%, 10.7%, 7.1%, and 0.4%, respectively. In total, three cases (0.5%) of pneumonitis grade 1 were reported. No fatal cardiac events were observed. One patient treated for right-sided breast cancer developed a myocardial infarction, while another patient treated for left-sided breast cancer was diagnosed with cardiac arrhythmia.

Univariate analysis

Because of the low number of events, univariate and multivariate analyses were only performed for RFP. In univariate analysis, significantly worse RFP was observed in patients with pathological tumour size larger than 2 cm (HR 3.94; 95% CI 2.11–7.34, $p < 0.001$), patients with more than 3 positive lymph nodes (HR 3.22; 95% CI 1.22–8.50, $p = 0.018$), grade III tumours (HR 2.90; 95% CI 1.56–5.41, $p = 0.001$), tumours not expressing oestrogen receptor (HR 3.23; 95% CI 1.70–6.14, $p < 0.001$), tumours with triple negative

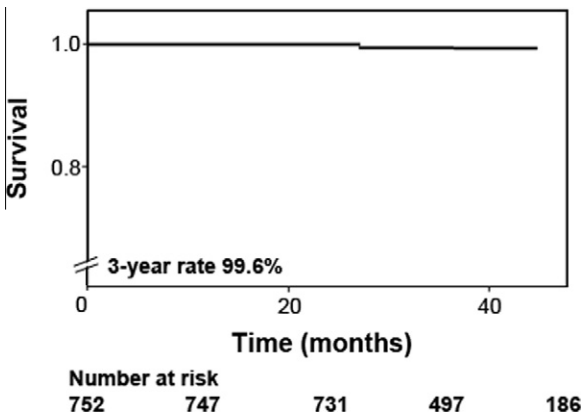

Fig. 1. Kaplan–Meier curve of local control and actuarial 3-year rate of included patients treated with breast conserving surgery and 3D-CRT-SIB after invasive breast cancer.

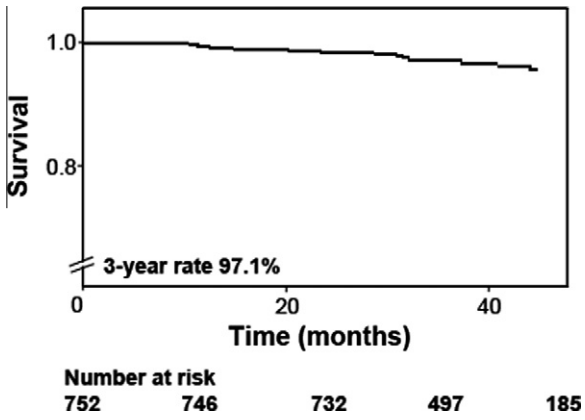

Fig. 2. Kaplan–Meier curve of overall survival and actuarial 3-year rate of included patients treated with breast conserving surgery and 3D-CRT-SIB after invasive breast cancer.

Table 3
Actuarial 3-year survival rates according to age at diagnosis and overall.

Endpoint	⩽50		>50		Total		
	%	(95% CI)	%	(95% CI)	*p*-Value[a]	%	(95% CI)
Local control	99.5	(99.4–99.5)	99.6	(99.5–99.6)	0.98	99.6	(99.5–99.6)
Locoregional control	99.0	(98.9–99.0)	99.2	(99.1–99.2)	0.61	99.2	(99.1–99.2)
Recurrence-free period	96.3	(96.2–96.3)	95.2	(95.1–95.2)	0.76	95.5	(95.4–95.5)
Overall survival	98.5	(98.4–98.5)	96.6	(96.5–96.6)	0.25	97.1	(97.0–97.1)

Abbreviations: CI: confidence interval.
[a] Compared with log-rank test.

receptor status (HR 4.02; 95% CI 2.06–7.84, $p < 0.001$) and those patients who received adjuvant chemotherapy (HR 2.14; 95% CI 1.15–3.99, $p = 0.02$) or regional RT (HR 2.98; 95% CI 1.25–7.14, $p = 0.01$). Young age was no risk factor for RFP, neither among patients of ⩽50 years (HR 1.12; 95% CI 0.56–2.24, $p = 0.76$), nor among patients ⩽40 years of age (HR 0.63; 95% CI 0.20–1.91, $p = 0.53$).

Multivariate analysis

Tumour size and triple negative receptor status were the only two independent prognostic factors for RFP (Table 4). Patients with tumours larger than 2 cm had worse RFP than patients with tumours smaller than 2 cm. Furthermore, RFP was impaired in patients with triple negative receptor status compared to those with non-triple negative status.

Excluding the secondary malignancies or non-breast cancer related deaths from the analysis did not change results and therefore both factors were not considered significant competing risks (data not shown).

Discussion

In this large consecutive series of patients treated with breast conserving surgery and hypofractionated 3D-CRT-SIB irradiation, local control at 3 years was 99.6%, with only a few cases of grade 2 or higher late toxicity. The 3-year LRC and OS were 99.2% and 97.1%, respectively.

In 2001, Bartelink et al. [13] published the results of the randomized EORTC study 22881-10882, with one of the largest series treated with whole breast irradiation and a sequential boost of 16 Gy ($n = 2661$). The radiotherapy boost was delivered in various ways (external beam electrons, photons or iridium-192 brachytherapy). Radiotherapy was generally not given with the use of modern 3D CT-based radiotherapy techniques. At 3 years of follow-up, LC and OS among patients who received a boost dose in that study were 97.9% (95% CI 97.6–98.2) and 93.8% (95% CI not reported), respectively. After publication of these results, whole breast irradiation with a sequential boost of 16 Gy was introduced as standard of care in the Netherlands. The current 3D-CRT based study shows somewhat higher LC rates compared to the EORTC study by Bartelink et al.

Table 4
Multivariate model of recurrence-free period.[a]

Characteristic	HR	(95% CI)	*p*-Value
Pathological T-stage			
T1	1		
T ⩾ 2	3.11	(1.57–6.17)	0.001[b]
Pathological N-stage			
N0	1		
N1	1.19	(0.56–2.56)	0.65
N2+	2.18	(0.76–6.25)	0.15
Differentiation grade			
I/II	1		
III	1.52	(0.70–3.31)	0.29
Triple negative[c]			
No	1		
Yes	3.03	(1.37–6.67)	0.006
Adjuvant chemotherapy			
No	1		
Yes	0.82	(0.38–1.77)	0.62

Abbreviations: HR: hazard ratio; CI: confidence interval.
[a] Adjusted for all covariates in the model.
[b] Bold values signify $p < 0.05$.
[c] Oestrogen receptor negative, progesterone receptor negative and human epidermal growth factor receptor 2 negative.

McDonald et al. recently reported on a series of 282 invasive breast cancer patients treated with Intensity-Modulated Radiation Therapy (IMRT)-SIB after breast conserving surgery [14], and found 8 ipsilateral in-breast LR and 4 RR after a median follow-up of 33 months. The 3-year LRC and OS were 97.1% and 97.0% (95% CIs not reported), respectively. The characteristics of the study population were more or less comparable with that of the present series. Hence, the 99.6% LC rate in this consecutive series of breast cancer patients is promising and in line with the results found by others. Acute skin toxicity reported by others was also comparable to the toxicity we observed in the first 90 patients treated with 3D-CRT-SIB at our institution [6].

Overall, our late toxicity rates seem to be acceptable; at 3 years, the incidence of moderate to severe (i.e., grade ⩾2) fibrosis in the breast was lower than the 20% observed in the EORTC study 22881-10882 [5]. Physician-rated late toxicity after the use of SIB-RT was reported in a small prospective non-randomized study by Raiyawa et al. [15]. In that study 60 patients were treated with whole breast irradiation (25 fractions of 2 Gy) combined with either a sequential electron boost of 5 fractions of 3 Gy (in total 15 Gy) or a SIB-electron boost of 25 fractions of 0.4 Gy (10 Gy in total) to the tumour bed [15]. At 7 months of follow-up, grade ⩾2 fibrosis was reported in 10% of patients, which is comparable to our results. No grade ⩾2 telangiectasia, breast oedema, or rib fractures were observed. Most importantly, the toxicities were comparable between the two studied groups.

Young age at diagnosis (⩽50 years) was no risk factor for disease progression or any other endpoint considered in current series of breast cancer patients treated with BCT. In several other studies, young age was associated with worse clinical outcome, such as LC and survival after both BCT and mastectomy [7–10,13,16]. The lack of impact of age on disease recurrence in our series could be

explained by a number of factors. The small number of events in our series may have limited the ability to detect differences between groups, but could also indicate a safe selection of patients for BCT. Furthermore, the increased use of adjuvant systemic therapy, particularly in high risk node-negative patients might explain this lack of impact of age. In an overview of the randomized trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), both single agent and polychemotherapy have been shown to improve LC and survival significantly, with the largest gain in the youngest age groups (i.e., patients <50 years) [17,18]. Finally, another factor might be the boost dose, which was given to all patients. In our series, all patients received a boost, uniformly applied, which has been shown to further decrease the risk of local recurrences [5].

Another explanation for the lack of impact of age in our series might be the strong association between triple negative receptor status and disease progression. Triple negative receptor status resulted in a threefold increase of disease progression risk. Triple negative receptor status is strongly associated with poor clinical outcome [19,20]. In general, young women have more frequently triple negative tumours [19,21]. This could therefore be the biological explanation for worse outcome related to young age [7–10,13,16]. The only study investigating the impact of age independently of triple negative status is a retrospective study of 375 breast cancer patients in which both triple negative disease and patients under 35 years of age were independent risk factors for any recurrence [22]. This study by Kwon et al. was hampered by the fact that 31.5% of the patients did not receive any radiotherapy after breast conserving surgery. Furthermore, it is not clear whether the other patients received a boost to the tumour bed. Therefore, part of the local recurrences, especially in young women might be caused by inadequate local treatment. This could explain the relation found between age and recurrence.

One disadvantage of our series is the relatively short follow-up with a median of 41 months. Although it is known that there is no plateau phase for in-breast recurrences, most true local recurrences develop in the first 3 to 4 years after treatment [23].

Next to application of the SIB in 3D-CRT, the SIB can be used combined with IMRT (IMRT-SIB). A potential advantage of the IMRT-SIB over 3D-CRT-SIB is the possibility of reducing the dose in organs at risk (OARs), such as the heart, lungs and the contralateral breast. However, others showed that, in general, the same reductions of calculated dose to these OARs could be achieved in 3D-CRT-SIB compared to IMRT-SIB [24–26]. The combination of easy implementation of the 3D-CRT-SIB without increasing the complexity and time involved with radiation treatment planning, the relatively mild acute skin toxicity [6] and the excellent results found in this series, justify the implementation of 3D-CRT-SIB as an alternative for breast-IMRT-SIB.

In conclusion, 3D-CRT-SIB as part of BCT results in excellent local control, LRC and OS rates even in the younger population without excess in long term toxicity. Although these results are promising, longer follow-up is required to further confirm these results.

Conflicts of interest statement

None declared.

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