Five year outcomes of hypofractionated simultaneous integrated boost irradiation in breast-conserving therapy: Patterns of recurrence


Abstract
In 2005, we introduced hypofractionated 3-dimensional conformal radiotherapy with a simultaneous integrated boost (3D-CRT-SIB) technique after breast-conserving surgery. In a consecutive series of 752 consecutive female invasive breast cancer patients (stages I-III) the 5-year actuarial rate for local control was 98.9%. This new technique gives excellent 5-year local control.

Introduction
In breast cancer, three-dimensional conformal radiotherapy with a simultaneous integrated hypofractionated boost (3D-CRT-SIB) technique can be applied as part of breast-conserving therapy (BCT). In 3D-CRT-SIB, breast and boost beams are combined in one integrated treatment plan and are given simultaneously. This technique was adopted as standard by our department in 2005. The technique and fractionation schedule have been described in more detail by van der Laan et al. Advantages of the 3D-CRT-SIB compared to the conventional sequential boost technique are increased dose homogeneity with less unintended excessive dose outside the boost area, in combination with a higher dose per fraction to the tumour bed, resulting in a shorter overall treatment time. Previously, we reported the 3-year outcomes, with a local control and overall survival of 99.6%, and 97.1%, respectively. In addition, no differences were observed with regard to late toxicity and cosmetic outcome as compared to those observed after the sequential boost technique.

The aim of this paper was to present the updated 5-year clinical outcomes and to study prognostic factors of recurrent disease in a large consecutive series of women with invasive breast cancer treated with 3D-CRT-SIB irradiation after breast-conserving surgery.

Patients and methods
From January 2005 to January 2008, 752 consecutive female invasive breast cancer patients (stages I–III) were treated with 3D-CRT-SIB as part of BCT at the department of Radiation Oncology of the University Medical Center Groningen. Patients were irradiated with 28 fractions of 1.8 Gy to the whole breast and 2.3 Gy (76%) or 2.4 Gy (in case of focal irradicality) to the surgical bed. Adjuvant chemotherapy, hormonal treatment, monoclonal antibodies and regional radiotherapy were prescribed according to the national guidelines. Indications for regional radiotherapy were more than 3 positive axillary lymph nodes or a positive apical lymph node. The apical lymph node was defined as the most cranially positioned lymph node in the axillary dissection specimen as marked by the surgeon. Indications for internal mammary nodes (IMN) radiotherapy were mediolateral located tumours with indication for regional radiotherapy, pathological positive IMN sentinel node, and sentinel node drainage to the IMN lymph nodes, which was not removed during surgery. Excluded were patients with previous invasive malignancies (except for non-melanoma skin cancer), previous thoracic irradiation, patients diagnosed with synchronous bilateral breast cancer, and patients treated with neo-adjuvant chemotherapy. Data were retrospectively collected and updated from the medical files. At diagnosis, median age was 58.4 (range 26-84) years.

Local recurrence (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 recurrence in the ipsilateral axillary, supraclavicular or internal mammary...
Results

Median follow-up was 60 (range 3-93) months. In total, 7 (0.9%) patients had an isolated LR, of which 5 (71%) were invasive and 2 (29%) pure DCIS histology. Four patients had an invasive isolated LR, located below the lumpectomy scar and within the boost planning target volume (PTV). The other three isolated local recurrences were at distance from the primary site, outside the boost PTV. All local recurrences were treated with a mastectomy. Eight months after primary treatment, one of these patients developed a second LR, and was treated with local excision, radiotherapy and hyperthermia. All these patients are alive without evidence of disease at last follow-up.

Five (0.7%) patients had an isolated RR, as first event. These isolated RRs were located in the ipsilateral axillary lymph nodes in 3 (60%) patients, in 1 (20%) patient in the supraclavicular nodal area, and in the IMN combined with supraclavicular nodal metastases in 1 (20%) patient. In 2 out of the 3 patients with an ipsilateral axillary lymph node recurrence, this recurrence was located in the cranial part of axilla level I. In the third patient, the ipsilateral regional recurrence was located in the interpector lymph nodes. Only the patient with the supraclavicular recurrence was node-positive at primary diagnosis (N1).

Two (0.3%) patients relapsed locally, regionally and at distant sites simultaneously. The first patient developed lymphangitis carcinomatosa with concurrent supraclavicular and distant metastases at 14 months of follow-up. The second patient presented with axillary and supraclavicular metastases, combined with skin metastases and distant metastases, 6.5 years after surgery. Both patients died of disease.

Three (0.4%) patients relapsed both regionally and distant simultaneously. The RRs were all located supraclavicular and in one patient combined with the IMN. One of these 3 (33%) patients died and the other 2 patients were disease-free at last follow-up. Initially, none of the patients with a RR was irradiated regionally.

In Table 2 all LRRs are listed according to intrinsic subtype.

Distant metastases as first event occurred in 39 (5%) patients, of which 19 (49%) died of these metastases. Seven patients with a LRR developed distant metastases and died. In total, 51 (7%) patients died during follow-up of which 26 (51%) were due to breast cancer.

Other causes of death were second cancers (n = 10; 20%), cardiovascular (n = 3; 6%), suicide (n = 1; 2%), liver cirrhosis (n = 1; 2%), pneumonia (n = 1; 2%), and unknown (free of disease at last follow-up) (n = 8; 16%).

Table 2. Patterns of failure in relation to intrinsic subtypes (n = 752)

<table>
<thead>
<tr>
<th>First event</th>
<th>Luminal (n %)</th>
<th>HER2-enriched (n %)</th>
<th>Basal (n %)</th>
<th>Unknown (n %)</th>
<th>Total (n %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence (LR)</td>
<td>7 (17.9)</td>
<td>0</td>
<td>2 (13.3)</td>
<td>0</td>
<td>9 (16.1)</td>
</tr>
<tr>
<td>Regional recurrence (RR)</td>
<td>5 (12.8)</td>
<td>0</td>
<td>3 (20.0)</td>
<td>0</td>
<td>8 (14.3)</td>
</tr>
<tr>
<td>Distant metastases (DM)</td>
<td>27 (69.2)</td>
<td>2 (100)</td>
<td>10 (66.7)</td>
<td>0</td>
<td>39 (69.6)</td>
</tr>
<tr>
<td>Total</td>
<td>39 (6.8)</td>
<td>2 (8.3)</td>
<td>15 (16.1)</td>
<td>0</td>
<td>56 (7.4)</td>
</tr>
<tr>
<td>No event</td>
<td>538 (93.2)</td>
<td>22 (91.7)</td>
<td>78 (83.9)</td>
<td>58 (100)</td>
<td>696 (92.6)</td>
</tr>
</tbody>
</table>

Abbreviations: HER2 = human epidermal growth factor receptor 2.

1 Luminal: ER positive and/or PR positive; HER2-enriched = ER negative, PR negative, HER2 positive = Basal: ER negative, PR negative, HER2 negative.

2 Two patients developed LR, RR and DM simultaneously.

3 Three patients developed RR and DM simultaneously.
The unadjusted 5-year actuarial rate of LC was 98.9% (95% CI 98.1-99.7), LRC 97.8% (95% CI 96.6-99.0), RFP 93.1% (95% CI 91.1-95.1), DMFS 94.2% (95% CI 92.4-96.0), DSS 96.8 (95% CI 94.4-98.2), and OS was 93.3% (95% CI 91.3-95.3), respectively. The survival curves for LC, DMFS, and OS are presented in Figure 1.

In total, 41 (6%) patients developed a secondary malignancy during follow-up. Eighteen out of these 41 (44%) patients had contralateral breast cancer. All tumours were invasive tumours. Other secondary tumour sites were ovaries in 1 (2%) patient; endometrium in 2 (5%); oesophagus in 1 (2%); other gastrointestinal tract in 9 (22%); lung in 5 (12%); and head and neck in 2 (5%) patients. Furthermore, 2 (5%) patients developed acute myeloid leukaemia, 1 (2%) patient a non-Hodgkin lymphoma, and another (2%) patient a glioblastoma multiforme. Ten patients died of the secondary malignancy (at other sites than the contralateral breast).

Patients with basal intrinsic subtype tumours, defined as oestrogen receptor negative, progesterone receptor negative, and human epidermal growth factor (HER-2) receptor negative (i.e., triple negative tumours) were at higher risk of recurrent disease, compared to patients with tumours of other subtypes (i.e., receptor positive breast cancer (HR 2.6, 95% CI 1.4-4.8, \(p = 0.002\)). Tumours with a diameter of more than 2 cm were associated with more recurrent disease (HR 2.7, 95% CI 1.5-4.7, \(p = 0.001\)). Furthermore, patients with more than 3 positive lymph nodes developed more recurrent disease than patients without positive lymph nodes (HR 2.7, 95% CI 1.2-6.3, \(p = 0.01\), NO as reference group). No increased risk of recurrent disease was observed between patients with 1-3 positive lymph nodes compared to patients with N0-disease (HR 0.9, 95% CI 0.5-1.7, \(p = 0.76\)).

![Kaplan-Meier curves with actuarial 5-year local control (LC) (dotted line), distant metastases free-survival (DMFS) (black), and overall survival (OS) (gray) (with corresponding 95% confidence intervals (CI)), including number at risk.](image)

**Figure 1.** Kaplan-Meier curves with actuarial 5-year local control (LC) (dotted line), distant metastases free-survival (DMFS) (black), and overall survival (OS) (gray) (with corresponding 95% confidence intervals (CI)), including number at risk.

**Discussion**

In this paper, the updated 5-year clinical outcomes are presented of a consecutive series of 752 patients treated with hypofractionated 3D-CRT-SIB for invasive breast cancer as part of BCT. Compared to other series in a comparable series of patients treated with an additional boost, these results are excellent. The 5-year results of the boost arm of the EORTC study 22881–10882, whole breast irradiation with a sequential boost, were 92.7% (95% CI 92.4-93.2) for LC, 91% (95% CI n.a.) for OS, and 87% (95% CI n.a.) for DMFS. The risk of developing a new primary in the contralateral breast is higher than that of an in-breast recurrence. Furthermore, 3 of the 7 local recurrences were at a distance from the primary tumour, and could therefore be considered as secondary primaries. This means that the applied treatment strategies are effective in preventing both true local recurrences, and second primaries in the ipsilateral breast.

Several factors can be attributed to the high LC rate of our hypofractionated 3D-CRT-SIB series. One of the explanations could be the introduction of CT-planning, resulting in better definition of the boost target volume. Furthermore, the SIB-fractionation schedule used in the present series was based on an equivalent dose for tumour control using an α/β ratio of 10. Current knowledge suggests a lower a/b ratio of 4.6 for tumour control, resulting in a higher biologically effective dose when compared to calculations with an a/b ratio of 10. This could result in a therapeutic advantage of present hypofractionated regimens compared to the standard fractionation. Another explanation for the high LC rate could be the increased use of systemic therapy in the present series. Additionally, in the 18 patients who developed contralateral breast cancer, only 1 patient was treated with hormonal and chemotherapy (data not shown). This supports the idea that new contralateral tumours in women with breast cancer could be prevented by the use of hormonal therapy.

Several studies suggested a relation between the occurrence of local recurrences and the development of distant metastases. By avoiding 4 local recurrences one breast cancer-related death can be prevented. Besides the improved LC, we also observed less distant metastases as seen in a decreased DMFS compared to the boost-study (94.2% vs. 87%).

In conclusion, the use of hypofractionated 3D-CRT-SIB as part of breast-conserving therapy results in excellent 5-year local control rates.

**References**


---

**Chapter 5**

3D-CRT-SIB: 5-year patterns of recurrence