Radiotherapy and Oncology 108 (2013) 269–272

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Breast cancer radiotherapy

Five year outcomes of hypofractionated simultaneous integrated boost irradiation in breast conserving therapy; patterns of recurrence

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ARTICLE INFO

Article history:
Received 12 May 2013
Received in revised form 26 August 2013
Accepted 26 August 2013
Available online 19 September 2013

Keywords:
Breast conserving therapy
Radiotherapy
Simultaneous integrated boost
Local control

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.

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 [1]. 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. [1]. 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 [1]. Previously, we reported the 3-year outcomes, with a local control and overall survival of 99.6%, and 97.1%, respectively [2]. In addition, no differences were observed with regard to late toxicity and cosmetic outcome as compared to those observed after the sequential boost technique [3].

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 [2]. 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 medial 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 (Table 1).

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

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http://dx.doi.org/10.1016/j.radonc.2013.08.037

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

Characteristic	n	(%)
Age at diagnosis (y)		
⩽50	204	(27.1)
>50	548	(72.9)
Pathologic T-stage		
T1	561	(74.6)
$T \geqslant 2$	191	(25.4)
Pathologic N-stage (n = 749)		
N0	521	(69.6)
N1	191	(25.5)
$N \geqslant 2$	37	(4.9)
Status resection margins (n = 744)		
Negative	635	(85.4)
(Focally) positive	109	(14.6)
Differentiation grade (n = 743)		
I/II	550	(74.0)
III	193	(26.0)
Oestrogen receptor (ER) (n = 721)		
Positive	595	(82.5)
Negative	126	(17.5)
Progesterone receptor (PR) (n = 719)		
Positive	514	(71.5)
Negative	205	(28.5)
HER2 (n = 695)		
Positive	69	(9.9)
Negative	626	(90.1)
Intrinsic subtypes[a]		
Luminal	577	(76.7)
HER2-enriched	24	(3.2)
Basal	93	(12.4)
Unknown	58	(7.7)
Adjuvant chemotherapy		
No	486	(64.2)
Yes	269	(35.8)
Adjuvant hormonal therapy		
No	461	(61.2)
Yes	292	(38.8)
Adjuvant trastuzumab		
No	715	(95.1)
Yes	37	(4.9)
Regional radiotherapy		
No	707	(94.0)
Yes	45	(6.0)

Abbreviations: HER2, human epidermal growth factor receptor 2.
[a] Luminal: ER positive and/or PR positive; HER2-enriched: ER negative, PR negative, HER2 positive; Basal: ER negative, PR negative, HER2 negative.

ipsilateral axillary, supraclavicular or internal mammary chain lymph nodes without clinical or radiologic evidence of distant metastases. Locoregional recurrence (LRR) was defined as either local or regional recurrence. Both LRR and distant metastases (recurrent disease) were included in recurrence-free period (RFP), and presented as 1-minus the cumulative incidence of recurrent disease. Only first events were considered in the described endpoints. Distant metastases free-survival (DMFS) was the exception, as all occurring distant metastases were included. Death of any cause was used for overall survival (OS). All endpoints were calculated from the date of diagnosis of primary breast cancer to the date of the event of interest or date of last follow-up.

Survival curves, including the unadjusted 5-year actuarial rates of local control (LC), locoregional control (LRC), RFP, DMFS, disease-specific survival (DSS) and OS were estimated with the Kaplan–Meier method. Multivariate Cox proportional hazard analysis with backward selection was used to study prognostic factors of RFP (recurrent disease). A two-sided p-value of <0.05 was considered statistically significant.

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 interpectoral 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%).

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 95.4–98.2), and OS was 93.3% (95% CI 91.3–95.3), respectively. The survival curves for LC, DMFS, and OS are presented in Fig. 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 gastro-intestinal 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