Med Oncol (2013) 30:518
DOI 10.1007/s12032-013-0518-7

ORIGINAL PAPER

Five-year results of a prospective case series of accelerated hypofractionated whole breast radiation with concomitant boost to the surgical bed after conserving surgery for early breast cancer

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Received: 22 January 2013 / Accepted: 18 February 2013 / Published online: 5 March 2013

Abstract Accelerated hypofractionation (HF) using larger dose per fraction, delivered in fewer fractions over a shorter overall treatment time, is presently a consistent possibility for adjuvant whole breast radiation (WBRT) after breast-conserving surgery for early breast cancer (EBC). Between 2005 and 2008, we submitted 375 consecutive patients to accelerated hypofractionated WBRT after breast-conserving surgery for EBC. The basic course of radiation consisted of 45 Gy in 20 fractions over 4 weeks to the whole breast (2.25 Gy daily) with an additional daily concomitant boost of 0.25 Gy up to 50 Gy to the surgical bed. Overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS) and local control (LC) were assessed. Late toxicity was scored according to the CTCAE v3.0; acute toxicity using the RTOG/EORTC toxicity scale. Cosmesis was assessed comparing treated and untreated breast. Quality of life (QoL) was determined using EORTC QLQ-C30/QLQ-BR23 questionnaires. With a median follow-up of 60 months (range 42–88), 5 years OS, CSS, DFS and LC were 97.6, 99.4, 96.6 and 100 %, respectively. Late skin and subcutaneous toxicity was generally mild, with few events > grade 2 observed. Cosmetic results were excellent in 75.7 % of patients, good in 20 % and fair in 4.3 %. QoL, assessed both through QLQ-C30/QLQ-BR23, was generally favorable, within the functioning and symptoms domains. Our study is another proof of principle that HF WBRT with a concurrent boost dose to the surgical cavity represents a safe and effective postoperative treatment modality with excellent local control and survival, consistent cosmetic results and mild toxicity.

Keywords Adjuvant whole breast radiotherapy · Breast cancer · Concomitant boost · Hypofractionation · Simultaneous integrated boost · Cosmesis

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Introduction

Adjuvant whole breast radiation (WBRT) after conservative surgery (BCS) is a standard of care in the combined modality treatment approach to early breast cancer (EBC),

reducing the risk of local recurrence and increasing overall survival [1, 2]. The addition of a boost dose to the tumor bed (TB) further raises local control [3]. Traditionally, WBRT has been delivered over 5 weeks employing a conventionally fractionated schedule (1.8–2 Gy daily) to a total dose of 50 Gy with a subsequent boost dose to the TB of 10–16 Gy for a total overall treatment time (OTT) of 6–7 weeks [1]. Hypofractionation (HF), delivering a lower nominal total dose in larger and fewer fractions, represents an option both for patients and healthcare providers' convenience as it allows for reduction in hospital visits and increase in patients turnover, globally decreasing treatment costs [4]. Radiobiologically, since in breast cancer the α/β ratio values for tumor and surrounding normal tissue substantially merge, a larger fraction size, with a concomitant slender total dose decrease, is likely to give a comparable tumor control probability with the same rate of expected late effects, compared to conventional fractionation [5]. Treatment acceleration (through HF), with OTT reduction below 6–7 weeks, might ameliorate cure rates narrowing the time for proliferation and repopulation [6]. The concomitant delivery of the TB boost along with WBRT [through different treatment plans in the concomitant boost (CB) approach or integrated within the same plan in the simultaneous integrated boost (SIB) solution] further reduces OTT, with an eventual ulterior gain [7]. We previously reported on preliminary data regarding feasibility, toxicity and cosmesis of WBRT after BCS for EBC, delivered through an accelerated hypofractionated schedule with CB to the TB [8]. We herein report on updated long-term results and survival of this prospective series.

Materials and methods

Between February 2005 and December 2011, we submitted a prospective series of 872 consecutive patients to an accelerated hypofractionated WBRT schedule with a CB to the TB, after BCS for EBC. The present study focused on long-term results of the cohort with early accrual (2005–2008) to report on patients with a median follow-up of 60 months. Furthermore, to provide reliable data on disease control and survival, we excluded ductal carcinoma in situ (DCIS) from the present analysis. Our sample size ended up in 375 patients. The Clinical Research and Ethical Review Board of our Institutional Hospital approved the study. Written informed consent was obtained from all patients.

Eligibility criteria

Eligibility criteria were as follows: histological diagnosis of breast adenocarcinoma, prior BCS (lumpectomy/quadrantectomy), negative resection margins (>3 mm) and pathological stage pT1–pT2, pN0–N1 according to American Joint Committee-Union Internationale Contre le Cancer staging system (AJCC-UICC; 6th edition); exclusion criteria were as follows: distant metastases, positive surgical margins, prior thoracic radiation, synchronous second primary tumor, age >80.

Setup, simulation and target definition

For setup, patients were positioned on a wingboard with both arms raised above the head and radiopaque markers along breast borders. Subsequently, the 5-mm-slice-thick axial images were acquired from the lower mandible aspect to lung bases; an isocenter was found in virtual simulation. The whole-breast clinical target volume (WB-CTV) encompassed breast palpable tissue, with a superior–inferior border within the extent of the radiopaque catheters. A uniform limit of 5 mm separated the WB-CTV from the skin surface and the thoracic wall. The whole-breast planning target volume (WB-PTV) was generated by adding a 5-mm isotropic margin around the WB-CTV. The definition of the TB was driven by radio-opaque clips placed during surgery. The CB clinical target volume (CB-CTV) was generated by adding a 5-mm isotropic margin around the TB; the consequent planning target volume (CB-PTV) required a further margin of 5 mm around the CB-CTV. The heart and ipsilateral lung were separately contoured as organs at risk: the heart was outlined to the pulmonary trunk superiorly, including pericardium and excluding major vessels.

Treatment schedule and delivery

The course of radiation consisted of 45 Gy, prescribed to the ICRU reference point dose to WB-PTV in 20 fractions (2.25 Gy daily) using 2 opposing 6 MV tangential fields; an additional dose of 0.25 Gy was concomitantly delivered (daily) to the CB-PTV, for an additional dose of 5 Gy with a direct 6 MV photon field. The cumulative nominal dose was 50 Gy in 4 weeks. The same isocenter was used for both tangents and boost field. This was also used as the normalization point. Acceptable levels of coverage for both WB-PTV and CB-PTV were as follows: 95 % of PTV was required to receive a minimum of 95 % dose and 99 % of PTV, to receive a minimum of 90 % dose. Radiation was delivered either immediately after BCS (<3 months) in low-risk patients or sequentially after adjuvant chemotherapy in high-risk cases. For radiobiological considerations and beam arrangement, see Cante et al. [8]. For setup verification purposes, tangential fields' portal images were weekly compared to digitally reconstructed radiographs (DRRs).

Follow-up, toxicity, cosmesis and quality of life assessment

During follow-up, patients were examined at 3 and 6 months and twice a year afterward. Surveillance for disease recurrence included a clinical examination at every time point, plain chest X-ray, mammography, complete blood cell count once a year; other radiological examinations were performed if needed. Acute skin toxicity was assessed at the completion of WBRT and after 3 months; late skin toxicity was scored from 6 months after radiation. The maximal detected toxicity was scored according to the Common Terminology Criteria for Adverse Events, version 3.0 for late effects; the RTOG/EORTC toxicity scale was employed for acute effects [9, 10]. We considered as skin toxicity these parameters: erythema, edema, desquamation, ulceration, hemorrhage, necrosis, telangiectasia, fibrosis-induration, hyperpigmentation, retraction and atrophy. Cosmetic results were assessed at the end of radiation and at every follow-up time point, using the standards set forth by the Harvard criteria, a cosmetic evaluation method based on a physician-rated scale consisting of different categories: excellent, good, fair or poor, comparing treated and untreated breast. At each examination, physicians were asked to judge the cosmetic results: an "excellent" score was assigned when the treated breast looked essentially the same as the contralateral; a "good" score for minimal but identifiable radiation effects; a "fair" score if significant radiation effects were readily observable; a "poor" score for radiation-induced severe late effects [11]. Late skin toxicity and cosmesis are referred to the time of examination. Quality of life (QoL) was assessed using the EORTC QoL-questionnaire QLQ-C30, an international instrument to measure general cancer QoL, quantifying patient's capacity to fulfill the activities of daily living. This tool incorporates 30 items exploring global health status/QoL and 5 functioning domains (physical, role, cognition, emotional, social) and assessing 9 symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial impact). All of the items were scored according to the standard scoring rules as in the EORTC QLQ-C30 Scoring Manual [12]. The raw scores from QLQ-C30 questionnaires were linearly transformed into standardized scores ranging from 0 to 100: higher scores in the global and functioning domains and lower scores within the symptom scales do stand for better QoL. With a breast cancer module, EORTC QLQ-BR23, we investigated QoL among our patients. This is an EORTC QLQ-C30 supplementary module targeted to breast cancer and developed to assess tumor site-related specific symptoms, treatment-related side effects and disease-specific QoL domains. It is composed of 23 items related to 4 functioning domains (body image, sexual functioning, sexual enjoyment, future perspective) and to 4 symptom scales (systemic therapies side effects, breast symptoms, arm symptoms, upset by hair loss). The scoring methods are similar to those of EORTC QLQ-C30. Both EORTC QLQ-C30 and QLQ-BR23 were assessed at the time of last examination.

Statistical analysis

Disease recurrence was defined as local (LR) if within the ipsilateral breast (any site) or overlying skin, regional (RR) if involving ipsilateral axillary, supraclavicular or internal mammary lymph nodes and systemic (DM) if arising elsewhere. All LR, RR and DM were considered for disease-free survival. Death of disease was defined as death due to disease. Death of any cause was considered for overall survival. Survival curves and actuarial rates of relapse were calculated using Kaplan–Meier method. The significance of clinical prognostic factors regarding both disease-free survival (DFS) and cancer-specific survival (CSS) was assessed by log-rank test. Multivariate analysis was performed using stepwise Cox proportional hazard regression models and related to DFS. A p value < 0.05 was considered significant. Stat View (version 5.0) was employed for analysis.

Results

The 375 patients included in the present analysis achieved a minimum follow-up of 42 months. Baseline patients' characteristics are detailed in Table 1. Most of the patients were aged >50 years with an invasive primary <2 cm in diameter (69.6 %), node negative (66.9 %), hormone sensitive (87.5 %), moderately differentiated (65.8 %) with ductal histology (58.7 %), low proliferation index (60.3 %) and without c-erb-B2 amplification (89.9 %). Most of the patients underwent quadrantectomy/lumpectomy and sentinel lymph node biopsy (73.3 %); 22 % underwent axillary dissection. We had 10.2 % of pNx cases since elderly patients (age >77 years) with T1 lesions and US-negative axilla were not submitted to sentinel lymph node biopsy. Almost 80 % received concomitant hormonal therapy, while 26 % were submitted to adjuvant chemotherapy. WBRT was always completed without interruptions due to clinical reasons. For the WB-PTV, 95.3 % of treatment plans achieved 95 % of the prescribed dose to at least 95 % of PTV and 98.1 % of treatment plans 90 % to at least 95 % of PTV (<2 % had WB-PTV coverage below 90 % isodose). On the contrary, for the CB-PTV, 83.2 % of treatment plans achieved 95 % of the prescribed dose to at least 95 % of CB-PTV and 90.3 % of treatment plans 90 % to at least 95 % of CB-PTV (almost 10 % of plans had

Table 1 Baseline characteristics

Patient characteristics	*N* (%)
Age (years)	
<50	45 (12)
>50	330 (88)
Pathological tumor stage	
pT1a	33 (8.8)
pT1b	79 (21)
pT1c	188 (50.1)
pT2	75 (20)
Pathological nodal stage	
pN0	251 (66.9)
pN1	86 (22.9)
pNx	38 (10.2)
Histology	
Ductal carcinoma	220 (58.7)
Lobular carcinoma	98 (26.1)
Mixed ductal/lobular	34 (9.1)
Papillary	10 (2.7)
Mucinous	4 (1.1)
Tubular	4 (1.1)
Other	5 (1.2)
Grading	
G1	64 (17.1)
G2	247 (65.8)
G3	64 (17.1)
Estrogen receptor	
Positive	328 (87.5)
>80 %	196 (52.3)
<80 %	143 (35.2)
Negative	47 (12.5)
Progesterone receptor	
Positive	295 (78.7)
>80 %	104 (27.7)
<80 %	191 (51)
Negative	80 (21.3)
c-erbB2	
Amplification	38 (10.1)
No amplification	337 (89.9)
Ki-67	
<20 %	226 (60.3)
20–40 %	88 (23.4)
>40 %	40 (10.7)
Not available	21 (5.6)
Vascular invasion	
Positive	45 (12)
Negative	304 (81)
Not available	26 (7)
Perineural invasion	
Positive	14 (3.7)
Negative	322 (85.9)
Not available	39 (10.4)
Surgery	
Quad/Lump	16 (4.3)
Quad/Lump + SLNB	275 (73.3)
Quad/Lump + SLNB + AD	84 (22.4)
Concomitant hormonal therapy	290/375 (77.3)
Tamoxifen based	138 (47.6)
Aromatase inhibitor based	144 (49.6)
LH-RH an. + Tamoxifen	8 (2.8)
CT	98/375 (26.1)
CMF	35 (35.7)
FEC	43 (43.9)
AC + TXT	15 (15.4)
Other	5 (5)
Target therapy	
Herceptin	38 (10.1)

Quad quadrantectomy, *Lump* lumpectomy, *SLNB* sentinel lymph node biopsy, *AD* axillary dissection, *an* analog, *CT* chemotherapy, *CMF* cyclophosphamide–methotrexate–fluorouracil, *FEC* fluorouracil–epirubicin–cyclophosphamide, *AC* doxorubicin, cyclophosphamide, *TXT* docetaxel

CB-PTV coverage below 90 % isodose, mainly in deep-seated tumor beds).

Pattern of failure, survival and prognostic factors

The median follow-up was 60 months (range 42–88). Among 375 patients, 9 patients died: 3 of breast cancer and 6 of non-cancer-related causes. Recurrence was observed in 13 patients: 9 patients developed distant metastasis (DM)—bone, liver, lung, brain—and 4 recurred regionally (RR) in the supraclavicular (2) or axillary (2) lymph nodes. No local relapse (LR) was observed by the time of last examination. Actuarial 5 years overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS) and local control (LC) were 97.6, 99.4, 96.6 and 100 %, respectively (Fig. 1). Table 2 shows the correlation between clinical variables and survival. Univariate analysis showed that tumor stage ($p = 0.00053$), grading ($p = 0.004$), hormonal status ($p = 0.005$), hormonal therapy ($p = 0.005$), chemotherapy ($p = 0.0125$) and Ki67 (<20 vs. >40 %; $p = 0.0001$) statistically significantly affected DFS. Concerning CSS, grading ($p = 0.016$), hormonal status and hormonal therapy ($p = 0.0038$), vascular invasion (0.0025) and Ki67 (<20 vs. >40 %; $p = 0.0004$) were found to be statistically significant. Considered as a linear parameter, Ki67 affected both DFS ($p = 0.00003$) and CSS ($p = 0.017$).

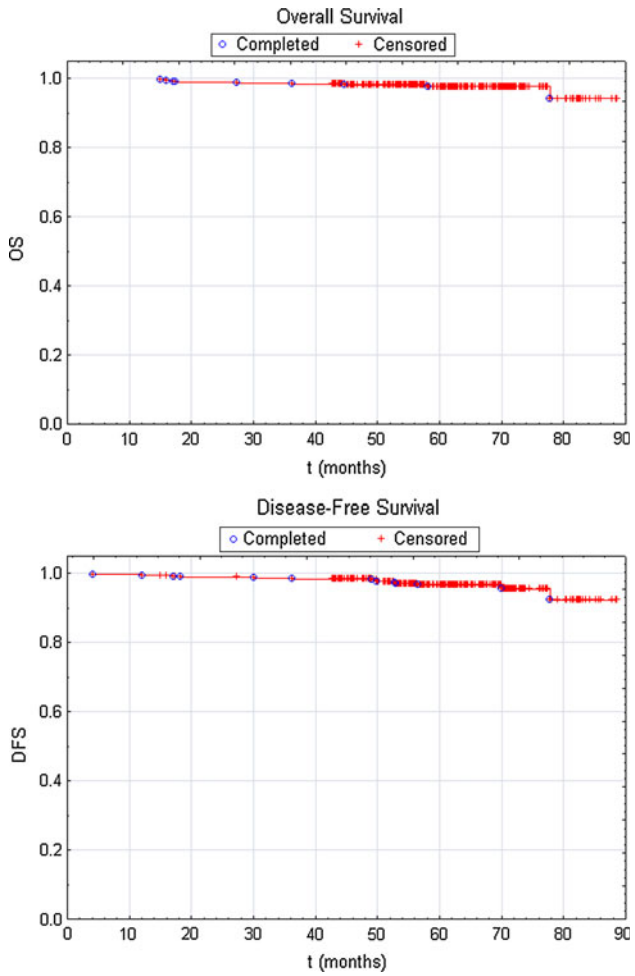

Fig. 1 Overall and disease-free survival

Toxicity

Acute toxicity was reported elsewhere [8]. Regarding late effects, no major lung and heart toxicities were detected. Late skin and subcutaneous toxicity was generally mild (Table 3): no events > grade 2 were observed. A grade 1 score was assessed for fibrosis/induration in 9.6 % of patients, grade 2 in 3.2 % and grade 3 in 1.1 %; moreover, grade 1 atrophy in 3.2 %, striae in 2.4 % and hyperpigmentation in 0.5 %; grade 1 telangiectasia in 2.1 % and grade 2 in 1.3 % of patients. Cosmetic results (Table 3) were excellent in 72.6 % of patients, good in 20 % and fair in 6.1 %. Poor cosmesis was observed in 5 patients (1.3 %), mainly due to surgical issues.

QoL

QoL is presented in Table 4, with mean scores and consequent standard deviations. The global health status (QLQ-C30) is 73.48 out of 100. According to QLQ-C30, functioning domains presents mean values around 90, except emotional functioning (74.42). Within symptoms domains, only pain, insomnia and constipation present values >10. Dealing with QLQ-BR23, functioning domains related to sexual life (sexual functioning and enjoyment) present scores <50 even at a median follow-up of 5 years; conversely, body image and future perspectives have mean values >70. Breast cancer-related symptoms present scores <10, except for systemic therapies (hormonal manipulation) with a mean value of 33.4.

Discussion

The delivery of daily doses higher than 1.8–2 Gy with hypofractionated schedule is a widespread option to perform WBRT after BCS for EBC [13]. Conventional fractionation is still the most explored radiotherapeutic strategy in this context, but HF has been used in several institutions for decades and tested in randomized controlled trials (RCTs) [14]. In the United Kingdom (UK), comprehensive guidelines by the UK's National Institute of Clinical Excellence (NICE) on the management of EBC recommended HF (specifically 40 Gy/15 fractions) as the standard choice [15]. Potential advantages of HF are directed to patients (convenience and costs), radiotherapy departments (patients' turnover) and global health systems (costs) [16]. Radiobiologically, breast adenocarcinoma has an α/β ratio (a numerical parameter representing cell sensitivity toward dose per fraction, accounting for the balance between non-repairable and repairable component of cell damage) around 4 Gy, close to late reacting normal tissues. A larger fraction size might achieve the same (even higher) probability of tumor control with a comparable rate of expected late effects, widening the therapeutic index [17]. Hitherto, 4 large phase III RCTs investigated HF versus conventional fractionation (50 Gy in 25 fractions over 5 weeks) in terms of local recurrence rate, side effects and breast cosmesis. The RMH/GOC trial randomized 1,410 patients with T1–T3/N0–N1 (after clear margins BCS) to 3 different WBRT regimens delivered over 5 weeks: standard fractionation versus 39 Gy/13 fractions (3 Gy daily) and 42.9 Gy/13 fractions (3.3 Gy/day). In this study, 75 % of patients received a direct electron field boost dose to the TB (14 Gy/7 fractions) [18]. The multi-institutional START A Trial enrolled 2236 women with a trial design similar to RMH/GOC unless a decreased daily dose (3.2–41.6 Gy/13 fractions) in the second experimental arm. In this study, 60.6 % of patients received extra-dose to the TB [19]. The START B Trial accrued 2215 with the same eligibility criteria as START A. The experimental arm accelerated treatment with 40 Gy/15 fractions over 3 weeks. Only 42.6 % of patients received a boost dose [20]. Finally, the Canadian Trial, updated with a median follow-up of

Table 2 Prognostic factors

Factor	*N*	Relapses	*p* value (log rank)	BC deaths	*p* value (log rank)	HR (95 % CI)	*p* value (Cox-regr)
Age							
<50	45	1	NS	1	NS	2.11 (0.79–4.91)	
≥50	330	12		2			
Tumor							
T1	300	6	0.0005	2	NS	4.38 (1.23–15.63)	0.022
T2	75	7		1			
Axillary nodes							
pN0	251	3	NS	1	NS	0.84 (0.22–3.18)	
pN1	86	10		2			
Grading							
G1–G2	311	7	0.004	1	0.016	0.88 (0.14–5.27)	
G3	64	6		2			
Hormonal status							
Positive	328	7	0.005	1	0.0038	0.36 (0.06–2.04)	
Negative	47	6		2			
HER2							
Positive	38	3	NS	0	NS	0.90 (0.17–4.69)	
Negative	337	10		3			
Vascular invasion							
Positive	45	3	NS	2	0.0025	2.04 (0.41–10.03)	
Negative	304	8		1			
Perineural invasion							
Positive	14	1	NS	0	NS	1.14 (0.09–14.55)	
Negative	322	10		3			
Hormonal therapy							
Yes	332	7	0.005	1	0.0038	0.36 (0.06–2.04)	
No	47	6		2			
Chemotherapy							
Yes	98	7	0.0125	2	NS	1.26 (0.31–5.20)	
No	277	6		1			
Axillary dissection							
Yes	84	3	NS	1	NS	0.85 (0.19–3.65)	
No	291	10		2			
Ki67							
<20 %	226	3	0.0001	0	0.0004	1.97 (0.79–4.91)	
20–40 %	88	4		1			
>40 %	40	6	(<20 vs. >40 %)	2	(<20 vs. >40 %)		

N number, *HR,* hazard ratio, *BC* breast cancer, *NS* not significant, *CI* confidence interval

10 years, randomized T1–T2 node-negative breast cancer patients with negative margins to receive 42.5 Gy/16 fractions over 3.5 weeks or standard fractionation, without any boost dose [21]. In terms of LC, all trials showed equivalency (or even superiority) between HF and standard schedule, as it is confirmed by the conclusion of the Cochrane review [22]. Concerning normal tissue toxicity and cosmesis, even if different measuring strategies were employed in the 4 studies, globally 25–40 % of patients experienced mild adverse effects, while 10 % had ≥ grade 2 side effects with medium to long-term observation, without fractionation influence [14]. For certain end points, HF had fewer adverse effects: a lower rate of change in skin appearance was found with HF in the START A and B trials [19, 20]. Late effects on ribs, heart, lung and brachial plexus were extremely rare. These data strongly support HF to deliver WBRT to reduce OTT. None of the 4 RCTs explored the use of the boost dose to the TB within

Table 3 Late toxicity and cosmesis

Parameters	Grade (%)			
	G1	G2	G3	G4
Induration-fibrosis	36 (9.6)	12 (3.2)	0	–
Atrophy	12 (3.2)	0	–	–
Telangiectasia	8 (2.1)	5 (1.3)	0	–
Hyperpigmentation	2 (0.5 %)	0	–	–
Striae	9 (2.4)	0	–	–
Ulceration	–	0	0	0

	Cosmesis			
Definition	Poor	Fair	Good	Excellent
	5 (1.3)	23 (6.1)	75 (20)	272 (72.6)

Table 4 Quality of life

Items QLQ-C30	Mean value (SD)
Global health status	73.48 (20.33)
Physical functioning	91.73 (10.15)
Role functioning	90.65 (18.45)
Emotional functioning	74.42 (19.80)
Cognitive functioning	91.36 (15.55)
Social functioning	87.76 (20.30)
Fatigue symptom	19.20 (18.40)
Nausea/vomiting	3.40 (9.80)
Pain	12.70 (18.80)
Dyspnea	6.20 (12.56)
Insomnia	13.60 (23.48)
Appetite loss	5.20 (14.36)
Constipation	14.62 (22.46)
Diarrhea	6.42 (15.62)
Financial difficulties	4.20 (11.28)
Items QLQ-BR23	
Body image	72.34 (21.32)
Sexual functioning	38.12 (25.15)
Sexual enjoyment	48.62 (16.38)
Future perspective	82.60 (24.42)
Systemic therapy side effects	33.43 (12.68)
Breast symptoms	9.80 (12.24)
Arm symptoms	6.30 (17.36)
Upset by hair loss	3.40 (10.80)

treatment protocol. The Canadian Trial had no boost. The UK trials delivered conventionally fractionated boost dose sequential to WBRT, according to institution discretion, with an increase in OTT (1–2 weeks). However, 2 RCTs provided evidence on the benefit of adjunctive dose to the TB in terms of LC (delivered with various modalities) [3, 23]. The incorporation of the boost dose within WBRT, with a concurrent delivery (CB or SIB approach) increases the time-saving benefit of HF in the WBRT phase, further reducing OTT. The cohort in our study is one of the few with long-term follow-up reporting results of HF in WBRT with a CB to the TB. Freedman et al. [24] (Fox Chase Cancer Center) accrued 75 patients (Tis-T2, clear resection margins) onto a phase II trial of photon-based WBRT delivered in 4 weeks to 45 Gy/20 fractions (2.25 daily) with an IMRT incorporated boost of 2.8 Gy daily to 56 Gy/20 fractions. Five-year LC was 97.3 %. Cosmesis, evaluated using patient- and physician-reported Breast Cancer Treatment Outcome Scale (BCTOS), was close to excellent with minimal difference between treated and untreated breasts. Chadha et al. (Beth Israel Medical Center) treated 160 EBC patients (Tis-T2, node negative, negative resection margin and chemotherapy-naïve) with accelerated HF delivering 40.5 Gy/15 fractions (2.7 Gy daily) to the whole breast (over 3 weeks; 19 days) with an adjunctive concurrent 0.3 Gy daily to the TB, to 45 Gy/15 fractions. With a median follow-up of 3.5 years, the 5-year OS and DFS were 90 and 97 %; local control was 99 %. No late toxicity higher than G2 according to LENT-SOMA scale was observed among patients with >2 years of follow-up[25]. Formenti et al. (NYU) enrolled 91 women on a single-arm prospective study of WBRT in prone position to 40.5 Gy/15 fractions (2.7 Gy daily) over 3 weeks. A SIB was delivered to the TB with IMRT to receive 45 Gy/15 fractions (3 Gy daily; 0.3 Gy boost extra-dose each day). With a median follow-up of 12 months, 1 recurrence, 2 acute grade 3 toxicities according to RTOG/EORTC (reversible grade 1–2 dermatitis in 67 % of patients) and no grade 3 late effects according to LENT-SOMA were observed (grade 1 fibrosis in 48 % of patients; grade 2 in 3 %) [26]. Finally, McDonald et al. reported 3-year outcome of a retrospective series of 354 patients (Stage I–III disease, mostly margin free; node positivity allowed) treated with IMRT-SIB consisting of 45 Gy/25 fractions (1.8 Gy daily) to the whole breast and 2.14 Gy each day to the TB concurrently, followed by a dedicated cavity boost of other 3 fractions (2.14 Gy) to 59.92 Gy. Grade 3 acute toxicity was <1 %, 3-year loco-regional recurrence was 2.8 % (among invasive breast cancers) and global breast cosmesis was good–excellent in 96.5 % [27]. Our schedule consisted of 45 Gy/20 fractions delivered to the whole breast (2.25 daily) and an adjunctive 0.25 Gy daily dose to the TB to a total nominal dose of 50 Gy (2.5 Gy daily). The whole course was given in 4 weeks (26 days). Assuming α/β ratio values of 4, 10 and 3 Gy for tumor control, early-responding tissues and late effects, our schedule carries BED_{2Gy} values of 81, 62.5 and 91.5 Gy. Theoretically, this is slightly less than an iso-effective dose regimen compared to WBRT delivered with conventional fractionation and sequential boost that shows BED_{2Gy} of 90, 72 and 100 Gy. However,

we assumed that the reduction in OTT (4 versus 6 weeks) in our study might compensate this issue. Our LC data seem to corroborate this hypothesis with excellent local control at a mature mean follow-up (60 months), even though our cohort includes a large number of patients with relatively low risk of recurrence (early stage, clear resection margins, positive hormonal status) which might lead to an intrinsic low rate of recurrence, not necessarily related to the supposed boost dose benefit. Nevertheless, the acute toxicity profile of our schedule is generally mild [8]. Late skin effects seem acceptable (maybe also due to the decrease in BED for sequelae) with no G3 toxicity and G2 fibrosis and telangiectasia comparable with other series [28]. Cosmesis seems consistent, although a physician-rated scale comparing the index breast with the contralateral breast, might be considered a limitation of our study. In fact, it is generally accepted that a photographic assessment of breast cosmesis (including post-surgical and pre-radiotherapy baseline documentation) is more objective, since it compares the appearance of the same breast and it takes into account surgery-related changes. QoL seems substantially unaffected by treatment on a long-term basis, even though a comparison with baseline scores is not available; however, our QoL scores are comparable to previously published experiences [29, 30]. In the UK, the IMPORT High Trial tested dose-escalated SIB-IMRT in women with higher than average risk of local recurrence, after BCS [31]. Similarly, in the United States, a Phase III RCT (namely RTOG 1005) just started patients' accrual, comparing HF WBRT and CB to conventionally fractionated standard radiation in the United States [32]. The present study provides a single-institution experience with mature follow-up time and assimilable design concept.

Conclusion

Our results provide another proof of principle; that HF to deliver WBRT with CB administration to the TB appears as a safe and effective postoperative treatment modality with excellent LC and survival, consistent cosmetic results and mild toxicity, but requires validation within large randomized controlled trials.

Conflict of interest No conflicts of interest to be declared.

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