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Title:

Prospective evaluation of weekly concomitant tumor bed boost with three-week hypofractionated whole breast irradiation in early breast cancer

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Running title:

Concomitant boost in early breast cancer

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Abstract

Objectives: A prospective study was conducted to assess the acute and late toxicity of hypofractionated whole breast irradiation with a weekly concomitant boost for women with early breast cancer (EBC).

Methods: Women with EBC who underwent breast-conserving surgery were eligible. A dose of 40Gy in 15 fractions over 3 weeks was delivered to the whole breast with a concomitant weekly boost to the post-operative cavity of 3Gy in 3 fractions. Toxicity was graded using the RTOG acute toxicity and RTOG/EORTC late toxicity scales.

Results: A total of 67 women were enrolled with a median age of 49 years (range 31–69). Median follow up was 25 months (range 11-34). Acute skin reactions included grade (G) 1 (n=47, 70%), G2 (n=10, 13%) and G3 (n=1, 1.5%). Late skin toxicity was observed in 13 patients (19%), all of whom experienced G1 toxicity only. On multivariable analysis, diabetes mellitus was predictive of acute skin toxicity (p=0.003), while age less than 50 years (p=0.029) and diabetes mellitus (p=0.013) were predictive of late skin toxicity.

Conclusions: Whole breast irradiation with concomitant weekly boost appears feasible and safe. Further investigation is required to fully evaluate this schedule as an alternative to conventional whole breast irradiation with a sequential boost.

Keywords: breast cancer, radiotherapy, tumour bed boost, hypofractionation

Manuscript:

Introduction

Breast radiotherapy is considered a standard adjuvant treatment for patients with early breast cancer (EBC) following breast-conserving surgery (BCS)[1]. Adjuvant whole breast radiotherapy has been shown to improve local control (LC) and overall survival, with a 70% reduction in recurrence risk[2,3] and a 9-12% reduction in risk of death[4-6].

Prospective randomized trials have demonstrated that the use of a tumor bed boost following whole breast irradiation reduces local recurrence risk, including in patients with negative surgical margins[7]. Traditionally, external beam radiotherapy consists of two phases: 50Gy delivered to the whole breast in 25 fractions over 5 weeks (5 fractions per week) followed by 10-16Gy delivered to the post-operative cavity in 5-8 fractions over 1-2 weeks[8].

Over the last few years, there has been renewed interest in hypofractionated whole breast irradiation (HF-WBI), defined as a larger daily dose delivered over a shorter time. This approach has important practical advantages and biological implications. The reduced total treatment time affords convenience for patients with decreased resource utilization. Furthermore, large randomized trials with 5- to 10-years follow-up have shown equivalence with regards to LC and cosmetic

outcome between HF-WBI and conventionally fractionated breast radiotherapy[9-11]. None of these trials included a simultaneous integrated boost; where boosts were included, these were delivered sequentially. In these studies, approximately 50% of patients received a tumour bed boost using conventional fractionation (2 Gy/fraction, total dose 10Gy)[10,11].

In order to intensify treatment, a simultaneous boost dose, concomitant or integrated, has been introduced into clinical practice, using 3-D conformal or intensity-modulated radiotherapy[12-15]. Preliminary results from previously published experiences of concomitant and integrated breast boost radiotherapy appear interesting and clinically feasible with acceptable acute toxicity[13,15,16,17].

The primary endpoints of this study were to assess the acute and late toxicity of a HF-WBI (3 week) schedule with a concomitant tumour bed boost delivered once weekly in women with EBC. Secondary endpoints included LC and overall survival. Patient and treatment characteristics predictive of toxicity were also investigated.

Methods

Patients

After institutional approval, this prospective study enrolled patients between January 2012 and December 2013. Inclusion criteria were: age ≥ 18 years, histologically proven unilateral EBC, prior conservative surgery (lumpectomy or quadrantectomy), pathological stage pT1-pT2, pN0 (AJCC-UICC, 6th edition) and negative surgical margins (≥2mm).

Patients with a previous history of contralateral breast irradiation, synchronous bilateral breast cancer, positive lymph nodes and/or connective tissue disorders were excluded.

Radiotherapy

Timing: Radiotherapy was planned either immediately after conservative surgery in patients at low risk of distant failure, or sequentially after adjuvant chemotherapy in patients at higher risk of progression. Risk classification was based on tumor size, grade, hormonal receptor status, HER-2 receptor status and age.

Radiotherapy fractionation: Whole breast irradiation consisted of 40Gy delivered in 15 fractions, 5 times a week, for 3 weeks. Once a week, immediately after whole breast irradiation, a concomitant photon 1Gy boost was delivered to the postoperative cavity, thus a total boost dose of 3Gy in 3 weekly fractions was delivered. The total treatment duration was 3 weeks and the total nominal dose to the lumpectomy area (considering cumulative dose to whole breast and surgical bed) was 43Gy.

Radiobiological equivalent dose: The linear-quadratic cell survival model[18] was used to calculate the biological equivalent doses received by breast, tumour bed and normal tissues using both conventionally fractionated whole breast radiotherapy with sequential boost, HF-WBI with weekly concomitant boost and, for comparison, HF-WBI without boost, as shown in Table 1. Here, α/β ratios of 4Gy for breast tumor response, 10Gy for acute responding normal tissues, 1.7Gy for late responding normal tissues (fibrosis) and 2.5Gy for vascular damage were employed[18].

Volumes of interest and treatment planning: A planning CT scan was performed for each patient positioned supine on a "wing-board" with both arms above the head. Radiopaque markers were used to delineate the clinically palpable breast tissue and visible surgical scars. Three tattoos were made on the thoracic skin to

enable accurate repositioning. The scan extended from the larynx to upper abdomen, including both lungs.

The whole breast clinical target volume (WB-CTV) included the glandular breast tissue from 3-5mm deep to the overlying skin to the surface of the pectoralis major and serratus anterior muscles. The whole breast planning target volume (WB-PTV) was a 5mm circumferential expansion around the WB-CTV and 10mm cranio-caudally.

The delineation of the post-operative cavity was guided by surgical clips, seroma or other surgical changes considered part of the cavity. The boost CTV was generated by adding a 5mm margin around the postoperative cavity, modified 3-5mm to exclude the skin surface, and extended to the surface of the pectoralis muscle and chest wall. The corresponding PTV was created by adding a further 5mm isotropic margin. For planning and dose evaluation, an evaluation PTV (eval-PTV) was defined by trimming the PTV 3-5mm from the skin surface. A forward-planned multi-segment tangential IMRT plan was generated, aiming for 100% coverage of the eval-PTV by the 95% isodose.

The heart and ipsilateral lung were considered OAR. The heart was contoured from the pulmonary trunk superiorly to its base and included the pericardium. Major blood vessels were excluded. The whole ipsilateral lung was contoured.

Follow-up and toxicity assessment: All patients underwent clinical examination before irradiation, weekly during treatment and every two months for the first year and every three months thereafter. Surveillance for disease recurrence included clinical examination at each time point, and baseline mammography at eight months from treatment completion and yearly thereafter. Acute toxicities were assessed in the first three months from start of RT and graded according to the RTOG acute toxicity scale. Late toxicity was scored ≥6 months from the end of treatment using the RTOG/EORTC scale for radiation-related toxicity.

Systemic therapy

All patients received adjuvant chemotherapy. In total, 43 patients (64.2%) received adjuvant chemotherapy followed by radiotherapy and 24 (35.8%) received radiotherapy followed by chemotherapy. Chemotherapy consisted of 5-fluorouracil, epirubicin and cyclophosphamide (FEC). Adjuvant hormonal therapy was indicated for all hormonal receptor-positive patients.

Statistical analysis

Data was analyzed using SPSS version 15 (Statistical Package for Social Sciences, IBM, Hampshire, UK). Multivariable logistic regression was performed to investigate potential patient and treatment characteristics predictive of acute and late skin toxicity. A $p<0.05$ was considered statistically significant.

Results

In total, 67 patients with operable invasive EBC were enrolled. Patients and tumor characteristics are listed in Table 2. In total, thirty-three patients (49%) were <50 years old. All patients underwent prior breast conservative surgery with ≥2 mm margins and level I/II axillary lymph node dissections. Invasive ductal carcinoma was the most common pathological subtype (95.5%). Over one quarter (n=19; 28.4%) of patients had tumors ≤ 2cm in diameter. Most tumors were histological grade 2 (58.2%). Adjuvant chemotherapy was received by 43 patients (64.2%) prior to radiotherapy and 24 (35.8%) following radiotherapy. Adjuvant hormonal therapy was prescribed in 47 patients after (chemo-)radiotherapy completion.

Median breast volume was 1593cc (range: 1150 – 2580cc). Median boost volume was 250cc (range: 87 – 445cc). In total, six patients had diabetes mellitus.

Median follow-up was 25 months (range: 11- 34). All patients completed the planned radiotherapy treatment. At the time of last follow-up, all patients were alive without evidence of locoregional recurrence or distant metastasis.

Acute toxicity

At the end of radiotherapy, mild acute reactions (grade 1) were observed in 47 patients (70.1%). Moderate skin toxicity (grade 2) was experienced by 13.4% of patients and only one patient, with diabetes mellitus, experienced a grade 3 reaction. The remaining 10 patients (14.9%) did not experience acute toxicity. The frequency of acute skin reactions is summarized in Table 3.

Factors predictive of acute radiation-induced skin toxicity

On univariable analysis, only diabetes mellitus was predictive of acute radiation-induced skin toxicity (p=0.0001). Age, breast volume, boost volume and chemotherapy prior to radiotherapy were not statistically significant. Multivariable analysis revealed that diabetes mellitus was the only significant factor predictive of acute toxicity (p=0.003, Odds ratio (OR) 95% CI: 4.997-30.82).

Late toxicity

The frequencies of late skin toxicity are reported in Table 4. Late grade 1 skin toxicity was observed in 13 patients (19.4%). There was no late toxicity >grade 1.

Factors predictive of late radiation induced skin toxicity

Age, breast volume, and diabetes mellitus were significant predictors of late toxicity (p=0.015, 0.049, and 0.0001 respectively). The use of chemotherapy prior to radiotherapy was non-significant (p=0.079). Multivariable analysis identified age <50 years (p=0.029, OR 95% CI =1.010 – 1.204) and diabetes mellitus (p= 0.013, OR 95% CI = 0.000 – 0.195) as predictive of late radiation-induced skin toxicity.

Discussion

The concept of hypofractionated radiation therapy for breast cancer has been addressed in multiple clinical trials given its potential radiobiological advantages because of the low α/β ratio of breast cancer. Studies have confirmed that adjuvant HF-WBI following breast-conserving surgery offers disease control rates and toxicity profiles equivalent to those obtained using conventional fractionation[10,11,19,20].

This approach could be advantageous for patients at higher risk of local recurrence[21], however concerns remain regarding the potential toxicity of hypofractionated treatment regimens when also including a boost dose. The ASTRO task force developed evidence–based guidelines for whole breast hypofractionated radiotherapy in clinical practice in 2011, and did not reach a consensus regarding a specific dose-fractionation schedule for the boost dose. Indeed, the task force concluded that ″on the basis of the published data and the collective expert opinion of the panel, boost doses of 10-16Gy in 2-Gy fractions or 10Gy in 2.5-Gy fractions were considered acceptable″[22].

Thus the optimal method of delivering a tumour bed boost with hypofractionated irradiation remains unclear. In prospective randomized trials, the use of a tumor bed boost following whole breast irradiation reduced the risk of local recurrence, including in margins negative patients[22]. Furthermore, an international survey demonstrated that 85% and 75% of American and European physicians respectively, would deliver a boost, including in the presence of negative margins[23].

Prospective trials of HF-WBI either did not employ a boost or delivered it at the discretion of the treating physician or according to departmental policy. Recent phase I–II trials investigating the role of a concomitant boost in HF-WBI have demonstrated the safety and short-term efficacy of this approach. Corvo et al.

treated 377 patients with EBC using conformal radiotherapy with a whole breast dose of 46Gy in 20 fractions and a concomitant weekly boost of 1.2Gy to the lumpectomy site to a total dose of 52Gy. Overall, 85% of patients experienced Grade 0-1 acute skin toxicity, 12% experienced Grade 2 and 3% developed grade 3 acute skin toxicity[24]. Another clinical study involving 65 EBC patients treated with HF-WBI (39Gy in 13 fractions in 3 weeks) plus a concomitant weekly boost to the lumpectomy cavity (3Gy in 3 fractions) reported that 52% of patients experienced grade 0 acute toxicity, 39% experienced grade 1 and 9% developed grade 2 acute toxicity. At six months, grade 1 sub-acute toxicity was observed in 34% of cases and only 6% of patients developed grade 2 toxicity[25]. In addition, with a median follow-up of 24 months, Chadha et al, reported no significant negative effects from HF-WBI and concomitant boost on breast cosmoses[26].

In this current study, 67 patients with operable EBC were treated using a hypofractionated external beam radiotherapy schedule of 40Gy in 15 fractions over 3 weeks to whole breast plus a concomitant weekly cavity boost of 3 Gy in 3 fractions. At the end of treatment, grade 1 skin toxicity was observed in 70.1% of patients, 13.4% developed grade 2 skin toxicity and only one patient, with diabetes mellitus, experienced grade 3 toxicity. There was no acute skin reaction in ten patients (14.9%). These results are similar to that observed in previous studies[24,25].

No late toxicity above grade 1 was observed in our study. This result is in accordance with other published data[27,28]. Additional studies have, however, reported late toxicities greater than grade 1[29]. This may be explained by the use of different toxicity assessment scales. In addition, skin fibrosis is commonly scored by visual examination and palpation based scales that are potentially influenced by physician inter-observer variability. Late skin toxicity was assessed in this study although cosmetic outcome was not specifically evaluated. While there were no late skin toxicities above grade 1, potentially inferring a minor impact of this treatment strategy on cosmesis, this should not be assumed in the absence of specific measures of cosmesis, which assess features beyond skin changes alone. The authors acknowledge that the lack of data regarding cosmetic outcome is a limitation of this current piece of work.

In this study, we analyzed the impact of treatment and patient related factors on the development of acute and late radiation toxicity (age, breast volume, previous chemotherapy and presence of diabetes mellitus). In the literature, patient age has been used as a selection criterion for a breast boost[30]. In this current study age <50 years was predictive of late skin toxicity ($p=0.029$, CI 1.010 – 1.204). While the rate of late toxicity was low, age should remain a consideration with regards to late effects.

Breast volume has previously been identified as a relevant factor for skin toxicity. In this current study, there was no increase in acute skin toxicity in large breasted women (i.e. larger WB-CTV) (p=0.209), similar to that observed in other trials [31,32,33]. In contrast, some authors have reported strong correlations between breast volume or size and severity of acute skin toxicity[34,35]. Possible explanations for this discrepancy may be the different criteria used to define breast volume and, more specifically, a large breast size, as well as the range of breast volumes included in different study cohorts. Dorn et al[32] found that breast volume was the only patient factor significantly associated with moist desquamation on multivariable analysis (p=0.01). Focal moist desquamation was experienced by 27.2% of patients with breast volume >2,500ml compared to only 6.34% of patients with breast volume <2,500ml (p=0.03). In this current study, median breast volume was 1593cc (range 1150 – 2580cc), and so breast volumes >2500cc were not well represented.

In this current study, the use of adjuvant chemotherapy prior to radiotherapy was not predictive of acute and late skin toxicity. In the past, chemotherapy has been reported to result in a worsening of long-term fibrosis and cosmetic outcome[36,37]. The impact of modern anthracycline-based regimens in patients treated with HF-WBI is unknown.

Diabetes mellitus was the only variable in this current study identified as a statistically significant predictor of acute skin toxicity on univariable (p<0.001) and multivariable (p=0.003, OR 95%CI = 5.00-30.82) analyses, similar to what has been observed in some other trials[38,39]. In contrast, other groups have reported no significant correlation between diabetes mellitus and acute skin toxicity[29]. Clearly, the number of patients with diabetes mellitus in our cohort (n=6, 9%) was low and not all diabetic patients are at equal risk. Literature review demonstrates that patients with type I diabetes may be at greater risk of radiation morbidity[39]. Additionally, Ferro et al, observed that patients receiving concurrent metformin and radiotherapy experienced an increased frequency of treatment breaks and desquamation[40]. The impact of diabetes mellitus, type I or II, and its treatments, on radiation-induced toxicity, therefore, requires further investigation.

Radiobiological comparisons of conventional and hypofractionated regimens, as shown in Table 1, suggest that the hypofractionated schedule employed here delivers a lower total dose to the breast and tumour bed and a similar or slightly lower dose to the normal late responding tissues. These doses, theoretically, could therefore result in lower rates of tumour control, as well as similar levels of, or slight reductions in, late toxicities. The clinical evidence to date, however, in terms of whole breast dose, suggests, as above, that HF-WBI regimens are equivalent in terms of both tumor control and toxicity[10,11,19,20]. Importantly, all of our patients had negative surgical margins, and mainly grade 1 or 2

tumours, and in this situation, it may be that a lower boost dose can provide adequate control, without excessive toxicity. In addition, all patients received chemotherapy, which may provide additional protection from relapse. Further evaluation, and longer follow-up, of patients treated with the schedule employed here, including the concomitant boost, is, however, required to more fully determine the safety and efficacy of this approach.

Outcomes from the recently closed to accrual RTOG 1005 phase III trial (40Gy in 15 fractions to whole breast with concomitant 3.2Gy per fraction boost to the tumour bed (total boost dose 48Gy in 15 fractions) vs. 50Gy in 25 fractions with sequential 12-14Gy in 2Gy per fraction tumour bed boost) are eagerly awaited, and will guide future practice[41]. Similarly, the ongoing phase III IMPORT-HIGH, IMRT MC-2 and UZB trials also investigate HF-WBI with concomitant tumour bed boosts, and will also help determine the optimal way to deliver breast and tumour bed radiotherapy[42-44].

Conclusion

Hypofractionated whole breast irradiation with concomitant weekly boost appears feasible and safe. Further research is required to demonstrate the efficacy of this schedule as an alternative option to standard sequential boost techniques.

Compliance with ethical standards

Funding: No funding was received for this study

Conflict of interest: Ali Hosni, Louise Murray, Aisling Barry, Basel Refky, Eman Awad, Ghada Ezzat Eladawei and Robert Dinniwell declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Table 1: Biological comparison between standard adjuvant radiotherapy schedule and explored weekly concomitant boost schedule

Radiotherapy schedule	BED tumor control (α/β = 4 Gy)		BED acute effect (α/β = 10 Gy)		BED fibrosis (α/β = 1.7 Gy)		BED vascular damage (α/β = 2.5 Gy)	
	WB	BS	WB	BS	WB	BS	WB	BS
50Gy in 25 fractions over 5 weeks, then 10Gy in 5 fraction sequential boost	75	90	60	72	109	131	90	108
40Gy in 15 fractions over 3 weeks with concomitant weekly 3Gy in 3 fraction concurrent boost	68	77	51	56	108	123	86	97
40Gy in 15 fractions over 3 weeks without boost	68	68	51	51	108	108	86	86

Abbreviations: BED: biologically equivalent dose; WB: whole breast; BS: tumor bed site.

Table 2: Patient and tumor characteristics

Characteristics	Total number=67	
	n	%
Median age (range)	49 (31 – 69)	
Diabetes mellitus	6	(9%)
Histological type		
Invasive ductal carcinoma	64	(95.5%)
Invasive lobular carcinoma	3	(4.5%)
Pathological T- stage		
T1	19	(28.4%)
T2	48	(71.6%)
Pathological N- stage		
N0	67	(100%)
Grading		
G1	8	(11.9%)
G2	39	(58.2%)
G3	20	(29.9%)
Oestrogen–Progesterone receptors		
Positive	47	(70.1%)
Negative	20	(29.9%)
HER-2 status		
Negative	57	(85.1%)
Positive	10	(14.9%)
Adjuvant chemotherapy	67	(100%)
Following radiotherapy	24	(35.8%)
Prior to radiotherapy	43	(64.2%)
Adjuvant hormonal therapy		
None	20	(29.9%)
Tamoxifen	33	(49.3%)
Aromatase inhibitor	14	(20.9%)

Table 3: Acute toxicity (based on RTOG acute toxicity skin scoring)

RTOG score	Patients *n*=67	%
Grade 0	10	14.9%
Grade 1	47	70.1%
Grade 2	9	13.4%
Grade 3	1	1.5%

Table 4: Late toxicity assessment (based on RTOG/EORTC scale)

RTOG/EORTC scale	Patients *n*=67	%
Grade 0	54	80.6%
Grade 1	13	19.4%