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ORIGINAL ARTICLE

Hypofractionated whole breast radiotherapy with or without hypofractionated boost in early stage breast cancer patients: a mono-institutional analysis of skin and subcutaneous toxicity

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Abstract

Background Our study evaluated skin and subcutaneous toxicity analyzing its correlation with patient- and treatment-related factors in a large mono-institutional series of women with early stage breast cancer treated with adjuvant hypofractionated whole breast radiotherapy (WBRT) with or without a sequential hypofractionated boost (HB).

Methods Two hundred and nineteen patients, median age 62 years, received adjuvant hypofractionated WBRT in 16 fractions to a total dose of 42.4 Gy. Patients with negative prognostic factors received a HB of 2.65 Gy for 4 or 5 (patients with focal positive surgical margins) fractions. Systemic adjuvant treatments were hormonal therapy (HT) and/or chemotherapy (CHT) and/or Trastuzumab. Toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE 4.03) scale at 5th, 10th, 16th, 20th day from the start of radiotherapy (RT) and 1, 6 and 12 months after the end of RT. Univariate and multivariate analysis estimated toxicity predictive factors.

Results No case of treatment interruption and no acute or late G3 toxicities occurred. In the univariate analysis HB administration resulted a risk factor for acute toxicity, while CHT administration and number of excised lymph nodes ≥ 10 resulted a risk factor for late toxicity. In the multivariate analysis none of the evaluated factors emerged a risk factor for acute and/or late toxicity.

Conclusions Our results confirmed that hypofractionated WBRT even followed by a HB resulted safe and well tolerated. Longer follow-up is warranted to estimate late toxicity and treatment outcomes.

Keywords Breast cancer · Hypofractionated whole breast radiotherapy · Hyprofractionated boost · Skin toxicity · Subcutaneous toxicity

Introduction

Whole breast radiotherapy (WBRT) is the standard treatment for patients with breast cancer after breast-conserving surgery (BCS) [1]. Conventional fractionation schedules consisted of 50 Gy delivered over 5 weeks followed or not by a boost dose of 10–16 Gy to the tumor bed. A boost dose is highly recommended in patients with negative prognostic factors for local relapse, particularly in young patients [2].

In the past, to reduce treatment time, to improve patient quality of life (QoL) and to optimize healthcare system, hypofractionated regimens were implemented. The radiobiological rationale for hypofractionation is based on the relatively low α/β for breast cancer, which was estimated to

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be 4.0 Gy, that is similar to the α/β for surrounding normal tissues [3]. Four large randomized controlled trials [3–9] showed that hypofractionated WBRT achieved equivalent disease control, cosmesis and toxicity compared to WBRT delivered with a standard fractionation. Since in the aforementioned randomized trials either a boost dose was not administered [9] or it was delivered with a standard fractionation [3, 4, 7, 8], data on toxicity and cosmetics results, when hypofractionated WBRT and hypofractionated boost (HB) were administered, are still lacking.

Prospective studies evaluating sequential [10–21] or concomitant HB [10, 17, 22–24] showed favorable outcomes and toxicity profiles. However, since data derived from randomized trials are lacking, the optimal boost dose, fractionation and timing (concomitant or sequential) in conjunction with hypofractionated WBRT has to be clearly defined with further studies. At our Institution a moderate hypofractionated schedule for WBRT (2.65 Gy for fraction for 16 fractions) and boost (2.65 Gy for fraction for 4 fractions) delivery was adopted since 2014 and toxicity data of the first 220 consecutive treated patients were recorded to evaluate the toxicity of this treatment schedule. The present prospective study is focused on the evaluation of potential patient- and treatment-related risk factors for skin and subcutaneous toxicity in a large mono-institutional series of women undergoing hypofractionated WBRT, with or without a sequential HB.

Materials and methods

From January 2014 to August 2015, two hundred and twenty consecutive females with early stage breast cancer treated with BCS and adjuvant RT were evaluated. All patients gave written informed consent to undergo RT and to accept that their anonymous data could be used for scientific studies. The study was conducted in accordance with the Helsinki declaration as revised in 2000. For the purpose of the present analysis, data regarding 219 patients, aged 34–88 years (median, 62 years), were evaluated since one patient failed to complete the the established follow-up period. Systemic treatment included hormonal therapy (HT) and/or chemotherapy (CHT) and/or Trastuzumab. The CHT regimen used was anthracycline- and taxane- based and HT consisted of tamoxifen and/or aromatase inhibitors.

Radiation treatment

Each patient received WBRT in 16 consecutive fractions of 2.65 Gy (5 fractions a week), to a total dose of 42.4 Gy. In patients with negative prognostic factors such as young age (< 50 years), positive nodes, negative hormonal receptors, HER2/neu and Ki67 overexpression or lymphovascular invasion (LVI), a sequential HB of 10.6 Gy in 4 fractions (2.65 Gy for fraction) was prescribed. In patients with focal positive surgical margins a HB of 13.25 Gy in 5 fractions (2.65 Gy for fraction) was administered. Each patient was positioned supine on a flat breast board immobilization device, with both arms raised above the head. Radiopaque wires identified palpable breast tissue. The computed tomography (CT) scans (Aquilion S16, Toshiba America Medical Systems, Inc. Tustin, CA, USA) were acquired from the mandibular angle to the diaphragm with 3 mm slice thickness and step. CT-images were then transferred to the treatment planning system (TPS, Pinnacle^3 Philips V 9.10, Philips Radiation Oncology Systems, Fitchburg, WI, USA). All patients received WBRT with (HB patients) or without (non HB patients) a boost to the tumor bed, none received regional nodal RT.

Organs at risk (OARs) and clinical target volumes (CTV breast and CTV boost) were countered following the Italian guideline atlas [25]. CTV boost contouring was performed with the aid of the following preoperative and postoperative information: preoperative imaging, surgical clips, seroma, surgical report and histopathology report. Contoured OARs were the ipsilateral lung and the heart (only for the patients with left-sided breast cancer). As prescribed by our internal guidelines, the planning target volume (PTV) of the breast (PTV breast) was obtained expanding the CTV breast 1 cm in all directions except the medial, where the expansion was 0.5 cm, and the PTV of the tumor bed (PTV boost) was obtained expanding the CTV boost 0.5 cm in all directions. To create the PTVevals, all PTVs were drawn back to 5 mm under the skin surface. In each patient a three-dimensional conformal RT (3D-CRT) treatment was planned on an isocentric technique with the Pinnacle^3 TPS. Beam energy was 6 MV, and/or 15 MV (used for large breasts). Two tangential, opposed, wedged half-beams were used. Gantry and collimator angles were adjusted, using the Pinnacle^3 TPS beam eye view, minimizing heart and lung irradiation while maximizing target volume coverage. Dynamic wedges in the opposing tangential beams were used to improve target dose distribution. To avoid hot spots, dose distribution was optimized by adding an extra tangent field with a manually generated multi-leaf collimator configuration (field-in-field). A dose distribution in the PTVeval of 95–107% according to ICRU criteria was obtained, trying to lower OARs doses as much as possible. The boost dose was delivered by multiple photon beams. OAR constraints used for planning were: for the ipsilateral lung V16 (that is the lung volume percentage receiving ≥ 16 Gy) < 20% and V20 (that is the lung volume percentage receiving ≥ 20 Gy) < 40%, for the heart (in left sided breast cancer patients) Dmean (that is the mean heart dose) < 4 Gy, D5% (that is the dose received by 5% of the heart volume) < 20 Gy and V8 (that is the heart volume percentage receiving ≥ 8 Gy) < 3%.

For set-up verifications purposes, according to our internal guidelines, portal images were taken before the treatment session, for two consecutive days and then once a week and were compared to digitally reconstructed radiographs (DRR) obtained from planned CT.

Toxicity evaluation

Acute and late toxicity were assessed using the Common Terminology Criteria for Adverse Events (CTCAE 4.03) scale [26]. Acute toxicity was monitored at 5th, 10th, 16th (last day of RT for non HB patients), 20th (last day of RT for HB patients) from the start of RT and then 1 month after the end of RT. Late toxicity was monitored 6 and 12 months after the end of RT.

Statistical analysis

Descriptive statistical analysis was carried out to calculate patient demographic and prognostic factors. The Shapiro–Wilk test was used to assess the normal distribution of data. Due to their asymmetric distribution the Mann–Whitney's *U* test was used for comparisons of continuous variables and the Chi-square test with Yates' correction or Fisher's exact test were used for comparisons of categorical variables. To find predictive factors for acute and late skin and subcutaneous toxicity, univariate and multivariate analysis were performed. As a first step in the univariate analysis patient related factors (hypertension, diabetes and collagenopathies) and treatment related factors (number of excised lymph nodes ≥ 10, CHT, HT and HB administration) were analysed considering not only patients with acute and/or late toxicity, but also any type of acute and late toxicity graded according to the CTCAE 4.03 scale. Trastuzumab was not considered since it was prescribed only in 7 patients (in 5 HB patients and in 2 non HB patients). In a second step, univariate and multivariate Cox proportional hazards regression models for acute and late toxicity investigated the effect of patient and treatment related factors on acute (considering for the analysis patients whit any toxicity scored from 5th from the start of RT to 1 months after the end of RT) and on late toxicity (considering for the analysis patients with any toxicity scored from 6 to 12 months after the end of RT). In the multivariate analysis only variables that showed at univariate analysis a p value ≤ 0.25 [27] were evaluated as potential risk factors for acute (considering for the analysis patients whit any toxicity scored from 5th from the start of RT to 1 months after the end of RT) and late (considering for the analysis patients with any toxicity scored from 6 to 12 months after the end of RT). All calculations were carried out with IBM-SPSS® version 23.0 (IBM Corp., Armonk, NY, USA, 2015). A two-sided p value < 0.05 was considered significant.

Results

Patient, tumor and treatment main characteristics are described in Table 1. HB was prescribed in 106 (48.4%) patients as follows: 102 received 10.6 Gy in 4 fractions, while 4 patients (with focal positive surgical margins) received 13.25 Gy in 5 fractions. As shown in Table 2 HB patients were at major risk of relapse and were more likely treated with adjuvant systemic therapies. Hypofractionated RT even with an additional sequential HB was well tolerated, since no case of treatment interruption due to acute toxicity and no G3 toxicities were documented. Toxicities are reported in Table 2 and in Fig. 1: G2 acute toxicities were 49/219 (22.4%) and G2 late toxicities were only 5/219 (2.3%). Is worth of notice that although 87.7% of patients developed acute toxicity, in 53.2% of them acute toxicities recovered, since no late toxicity was detected. On the other hand late toxicity occurred in 25% of women that did not experience acute toxicity. In particular, 54.1% of HB patients with acute toxicity developed also late toxicity, while 39.8% of non HB patients with acute toxicity had also late toxicity.

Tables 3 and 4 show, respectively, univariate analysis for acute and late toxicity considering the number of patients that experienced toxicity and type of toxicity (according to CTCAE 4.03 scale) registered at 5th, 10th, 16th, 20th from the start of RT and at 1 month after the end of RT (acute toxicity) and after 6 and 12 months from the end of RT (late toxicity). The first detailed univariate analysis showed that collagenopathies, diabetes, number of excised lymph nodes ≥ 10, CHT and HB administration significantly increased acute toxicity (Table 3), while hypertension, collagenopathies, number of excised lymph nodes ≥ 10, CHT and HB administration significantly increased late toxicity (Table 4). Furthermore, a major rate of late toxicity occurred in patients with a larger CTV boost volume (data not shown) both at 6 months (median CTV boost volume 22.270 cc, range 2.23–95.73 cc, vs. 16.34 cc, range 2.81–68.85 cc, $p = 0.024$) and at 12 months after the end of RT (median CTV boost volume 25.09 cc, range 9.59–95.73 cc vs. 16.34 cc, range 3.57–68.85 cc, $p = 0.015$).

Univariate analysis results for acute (including all the patients that experienced any toxicity from 5th from the start of RT to 1 month after the end of RT) and late toxicity (including all the patients that experienced any toxicity from 6 to 12 months after the end of RT) are reported in Table 5.

As shown in Table 6 HB administration emerged as a risk factor for acute skin and subcutaneous toxicity ($p = 0.044$), while CHT ($p = 0.22$) and number of excised lymph nodes ≥ 10 ($p = 0.21$), administration emerged as a

Table 1 Patient, tumor and treatment characteristics

	All pts ($n=219$)	HB pts ($n=106$)	%	Non HB pts ($n=113$)	%	p
Median age (years)	62 (range 34–88)	55 (range 34–85)	–	67 (range 45–88)	–	**0.0001**
Stage						
0	34	4	3.8	30	26.5	**0.0001**
I	119	53	50	66	58.4	
II	66	49	46.2	17	15.1	
Lymphonodal status						
Negative	170	68	64.2	102	90.3	**0.0001**
Positive	49	38	35.8	11	9.7	
Lymph nodes excised						
<10	181	74	69.8	107	94.7	**0.0001**
≥ 10	38	32	30.2	6	5.3	
Histology						
DCIS	35	4	3.8	31	27.4	**<0.0001**
Infiltrating tumors	184	102	96.2	82	72.6	
Grading						
1	55	18	17	37	32.7	**0.006**
2	96	53	50	43	38.1	
3	45	28	26.4	17	15	
Not determined	23	7	6.6	16	14.2	
Hormonal status						
Positive	182	92	86.8	90	79.6	0.712
Negative	19	11	10.4	8	7.1	
Not determined	18	3	2.8	15	13.3	
Ki-67						
$<14\%$	107	47	44.3	60	53.1	**0.005**
$\geq 14\%$	84	55	51.9	29	25.7	
Not determined	28	4	3.8	24	21.2	
Her2-Neu						
Positive	11	8	7.5	3	2.7	0.254
Negative	173	94	88.7	79	69.9	
Not determined	35	4	3.8	31	27.4	
LVI						
Positive	22	18	17	4	3.5	**0.002**
Negative	197	88	83	109	96.5	
HT	172	92	86.8	80	70.8	**0.007**
CHT	46	42	39.6	4	3.5	**<0.0001**
Trastuzumab	7	5	4.7	2	1.8	0.268
Time from BCS to RT (weeks)	16.9 (range 8–43.4)	18.95 (range 8–43.4)	–	16 (range 8.1–37.4)	–	**0.0001**
CTV breast volume (cc)	704.516 (range 129.126–2170.36)	717.195 (range 224.948–2170.36)	–	695.912 (range 129.126–2086.32)	–	0.952
CTV boost volume (cc)	18.98 (range 2.23–95.73)	18.98 (range 2.23–95.73)	–	–	–	–
CTV boost volume ratio	35.77 (range 12.82–192.90)	–	–	–	–	–

The bold is related to the significant results

pts patients, *HB* hypofractionated boost, *HT* hormonal therapy, *CHT* chemotherapy, *BCS* breast-conserving surgery, *DCIS* ductal carcinoma in situ, *LVI* lymphovascular invasion, *RT* radiotherapy, *CTV* clinical target volume

Table 2 Acute and late toxicity

	No. of pts with toxicity	%		Dry skin	%	Hyperpigmentation	%	Induration/fibrosis	%	Pruritus/itching	%	Desquamation	%	Rash: dermatitis	%	Telangiectasia	%	Skin ulceration	%	Burn	%	Edema	%
Acute toxicity																							
Toxicity at 5th day	35	16	G1	–	–	–	–	–	–	2	0.9	1	0.5	21	9.6	–	–	–	–	–	–	16	7.3
			G2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	0.5
Toxicity at 10th day	84	38.4	G1	1	0.5	4	1.8	–	–	2	0.9	1	0.5	75	34.2	–	–	–	–	–	–	17	7.8
			G2	–	–	–	–	–	–	–	–	–	–	1	0.5	–	–	–	–	–	–	1	0.5
Toxicity at 16th day	155	70.8	G1	1	0.5	8	3.7	1	0.5	11	5	12	5.5	130	59.4	–	–	1	0.5	–	–	19	8.7
			G2	–	–	–	–	–	–	–	–	–	–	14	6.4	–	–	–	–	–	–	–	–
Toxicity at 20th day	166	75.8	G1	2	0.9	8	3.7	1	0.5	12	5.5	20	9.1	133	60.7	–	–	2	0.9	3	1.4	24	11
			G2	–	–	1	0.5	–	–	–	–	1	0.5	25	11.4	–	–	–	–	–	–	–	–
Toxicity at 1 month	150	68.5	G1	8	3.7	118	53.9	9	4.1	4	1.8	14	6.4	34	15.5	–	–	–	–	1	0.5	20	9.1
			G2	–	–	3	1.4	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2	0.9
Late toxicity																							
Toxicity at 6 months	87	39.7	G1	4	1.8	36	16.4	30	13.7	1	0.5	2	0.9	9	4.1	–	–	1	0.5	–	–	36	16.4
			G2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2	0.9
Toxicity at 12 months	46	21	G1	3	1.4	17	7.8	14	6.4	–	–	–	–	1	0.5	–	–	–	–	–	–	26	11.9
			G2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3	1.4

N number, *pts* patients, *G1* grade 1, *G2* grade 2

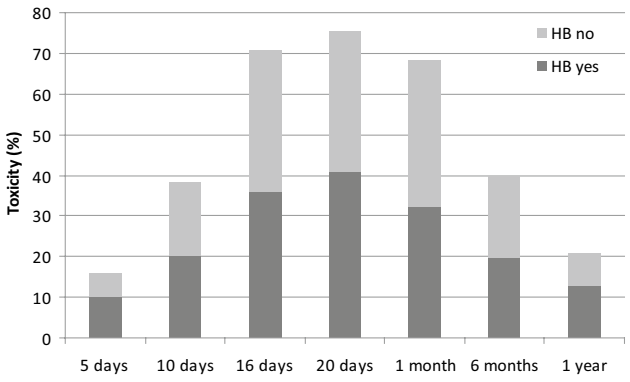

Fig. 1 Acute and late toxicity. *HB* hypofractionated boost

risk factor for late skin and subcutaneous toxicity. However, none of the evaluated variables included the multivariate analysis resulted significantly related to acute or late skin and subcutaneous toxicity (Tables 5, 6).

Discussion

Hypofractionated WBRT is widely used but, at present, the administration of a HB boost after hypofractionated WBRT and the timing relative to WBRT (concomitant or sequential) is a major issue of debate. Our prospective study was designed with the aim to contribute to the pivotal issue of toxicity evaluation of hypofractionated WBRT in conjunction with a sequential HB. We decided to focus our attention on skin and subcutaneous toxicity, since acute skin toxicity can lead to treatment interruptions and pain, while late skin and subcutaneous toxicity could strongly impair cosmesis and QoL.

Our results were in accordance with literature data [13, 16, 19, 28], confirming that hypofractionated WBRT even in conjunction with a sequential HB is well tolerated. In particular, no G3 overall acute or late toxicities and no treatment interruptions occurred. In our opinion, the favorable toxicity profile of our series is probably due to the treatment planning accuracy, resulting in particularly low dose distribution inhomogeneities. Literature data, in fact, reported that a higher incidence of acute skin toxicity is linked to dose distribution inhomogeneities, particularly if located under the skin surface [28]. Furthermore, in a recent paper [29] a significant correlation between acute toxicity and breast volumes > 500 cc was found, while in our series, despite patient breast volumes were quite large (median 704.516 cc, range 129.126–2170.36 cc), no relation between acute or late toxicity and breast volume emerged. In the first detailed univariate analysis in HB a significant increase in acute toxicity and in late toxicity 6 months from the end of RT occurred, but it is worth of notice that recovered as late toxicity was not significantly increased 12 months after the end of RT (Table 4). Moreover, it should be noted that in this first detailed analysis in HB patients a major rate of acute toxicity at 5th day of RT and a major rate of edema at 10th day of RT were recorded (Table 3). In our opinion, a major rate of toxicity occurred in HB patients since more HB patients underwent CHT (Table 1), which is a well-known risk factor for skin and subcutaneous toxicity [30], while a major rate of edema was documented, since a higher number of lymph nodes was removed in HB patients (Table 1) compared to non HB patients.

To our knowledge, at present, this is the only prospective study that evaluated by univariate analysis each type of toxicity at each time point during RT and throughout the follow-up period. This detailed toxicity analysis was carried out since it could be very useful to better define risk factors related to a specific type of skin and/or subcutaneous toxicity, allowing physicians to prevent and promptly treat any incoming toxicity in each patient during RT and throughout the follow-up period. In the univariate analysis, performed evaluating together patients with any acute toxicity (scored from 5th day of RT to 1 months after the end of RT) and patients with any late toxicity (scored from 6 to 12 months after the end of RT), HB administration resulted a risk factor for acute toxicity, while CHT and number of excised lymph nodes ≥ 10 were a risk factor for late toxicity. However, it is worth of notice that in the multivariate analysis none of the evaluated variables emerged as significantly related to skin and/or subcutaneous toxicity, confirming that hypofractionation with or without HB resulted safe, even in patients treated with CHT.

Results of prospective trials analyzing toxicity of hypofractionated WBRT schedule with a sequential HB (administered in 3–6 fractions) and potential predictive factors for toxicity [13, 15, 16, 18–21] are reported below. Briefly, De Antonio et al. [15] evaluated, with a median follow up of 15 months, 85 patients treated with 45 Gy in 20 fractions and with a boost of 9 Gy in 3 fractions (delivered with electrons) showing, unlike our results, a significant correlation of breast volumes with acute toxicity. In a second report, De Antonio et al. [16] reported data on the same patient series showing, at 8 years of follow-up, that breast volume was not a risk factor for late toxicity.

Sanz et al. [13], reported data on 362 patients, with a median follow-up of 4.5 years, treated with 40.05 Gy in 15 fractions followed by a boost dose of 8.01 or 16.02 Gy (2.67 Gy for fraction), in patients at intermediate (151 cases) or high risk of relapse (194 cases), respectively. In accordance with our results, they demonstrated a significant correlation between boost volumes and any late toxicity, showing that the absolute boost volume cut-off value for chronic toxicity risk was 55 cc.

Table 3 Predictive factors for acute skin and subcutaneous toxicity: univariate analysis

	Toxicity at 5th day					Toxicity at 10th day					Toxicity at 16th day					Toxicity at 20th day					Toxicity at 1 month				
	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*
Hypertension																									
No. of pts with toxicity	19/92	20.7	16/127	12.6	0.156	35/92	38.0	49/127	38.6	0.999	63/92	68.5	92/127	72.4	0.627	66/92	71.7	100/127	78.7	0.301	70/92	76.1	84/127	66.1	0.150
Dry skin	0/92	–	0/127	–	–	0/92	–	1/127	0.8	0.999	0/92	–	1/127	0.8	0.999	1/92	1.1	1/127	0.8	0.999	5/92	5.4	3/127	2.4	0.285
Hyperpigmentation	0/92	–	0/127	–	–	2/92	2.2	2/127	1.6	0.999	6/92	6.5	2/127	1.6	0.072	5/92	5.4	4/127	3.1	0.497	54/92	58.7	71/127	55.9	0.784
Induration/fibrosis	0/92	–	0/127	–	–	0/92	–	0/127	–	–	1/92	1.1	0/127	–	0.420	1/92	1.1	0/127	–	0.420	5/92	5.4	4/127	3.1	0.496
Pruritus/itching	1/92	1.1	1/127	0.8	0.999	1/92	1.1	1/127	0.8	0.999	5/92	5.4	6/127	4.7	0.999	4/92	4.3	8/127	6.3	0.765	1/92	1.1	3/127	2.4	0.641
Desquamation	0/92	–	1/127	0.8	0.999	1/92	1.1	0/127	–	0.420	6/92	6.5	6/127	4.7	0.782	9/92	9.8	12/127	9.4	0.999	6/92	6.5	8/127	6.3	0.999
Rash: dermatitis	12/92	13.0	9/127	7.1	0.213	32/92	34.8	44/127	34.6	0.999	57/92	62.0	77/127	60.6	0.953	63/92	68.5	95/127	74.8	0.380	18/92	19.6	17/127	13.4	0.296
Teleangiectasia	0/92	–	0/127	–	–	0/92	–	0/127	–	–	0/92	–	0/127	–	–	0/92	–	0/127	–	–	0/92	–	0/127	–	–
Skin ulceration	0/92	–	0/127	–	–	0/92	–	0/127	–	–	0/92	–	1/127	0.8	0.999	1/92	1.1	1/127	0.8	0.999	0/92	–	0/127	–	–
Burn	0/92	–	0/127	–	–	0/92	–	0/127	–	–	0/92	–	0/127	–	–	1/92	1.1	2/127	1.6	0.999	1/92	1.1	0/127	–	0.420
Edema	10/92	10.9	7/127	5.5	0.227	7/92	7.6	11/127	8.7	0.975	9/92	9.8	10/127	7.9	0.801	10/92	10.9	14/127	11.0	0.999	9/92	9.8	14/127	11.0	0.942
Collagenopathies																									
No. of pts with toxicity	2/4	50.0	33/215	15.3	0.129	3/4	75.0	81/215	37.7	0.159	2/4	50.0	153/215	71.2	0.076	2/4	50.0	164/215	76.3	0.292	2/4	50.0	152/215	70.7	0.422
Dry skin	0/4	–	0/215	–	–	0/4	–	1/215	0.5	0.981	0/4	–	1/215	0.5	0.981	0/4	–	2/215	0.9	0.963	0/4	–	8/215	3.7	0.861
Hyperpigmentation	0/4	–	0/215	–	–	1/4	25.0	3/215	1.4	0.072	0/4	–	8/215	3.7	0.999	0/4	–	9/215	4.2	0.844	0/4	–	124/215	57.7	**0.034**
Induration/fibrosis	0/4	–	0/215	–	–	0/4	–	0/215	–	–	0/4	–	1/215	0.5	0.981	0/4	–	1/215	0.5	0.981	1/4	25.0	8/215	3.7	0.164

Table 3 (continued)

	Toxicity at 5th day					Toxicity at 10th day					Toxicity at 16th day					Toxicity at 20th day					Toxicity at 1 month				
	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*
Pruritus/itching	0/4	–	2/215	0.9	0.963	0/4	–	2/215	0.9	0.963	1/4	25.0	10/215	4.7	0.200	0/4	–	12/215	5.6	0.797	0/4	–	4/215	1.9	0.928
Desquamation	1/4	25.0	0/215	–	**0.018**	0/4	–	1/215	0.5	0.981	0/4	–	12/215	5.6	0.999	0/4	–	21/215	9.8	0.666	0/4	–	14/215	6.5	0.769
Rash: dermatitis	1/4	25.0	20/215	–	0.381	2/4	50.0	74/215	34.4	0.553	2/4	50.0	142/215	66.0	0.541	2/4	50.0	156/215	72.6	0.377	1/4	25.0	34/215	15.8	0.625
Teleangiectasia	0/4	–	0/215	–	–	0/4	–	0/215	–	–	0/4	–	0/215	–	–	0/4	–	0/215	–	–	0/4	–	0/215	–	–
Skin ulceration	0/4	–	0/215	–	–	0/4	–	0/215	–	–	0/4	–	1/215	0.5	0.981	0/4	–	2/215	0.9	0.963	0/4	–	0/215	–	–
Burn	0/4	–	0/215	–	–	0/4	–	0/215	–	–	0/4	–	0/215	–	–	1/4	25.0	2/215	0.9	0.055	0/4	–	1/215	0.5	0.982
Edema	0/4	–	17/215	7.9	0.722	0/4	–	18/215	8.4	0.708	1/4	25.0	18/215	8.4	0.345	0/4	–	24/215	11.2	0.626	0/4	–	23/215	10.7	0.639
Diabetes																									
No. of pts with toxicity	1/15	6.7	34/204	16.7	0.339	3/15	20.0	81/204	39.7	0.136	9/15	60.0	146/204	71.6	0.359	10/15	66.7	156/204	76.5	0.406	12/15	80.0	142/204	69.6	0.421
Dry skin	0/15	–	0/204	–	–	0/15	–	1/204	0.5	0.931	0/15	–	1/204	0.5	0.931	0/15	–	2/204	1.0	0.867	1/15	6.7	7/204	3.4	0.535
Hyperpigmentation	0/15	–	0/204	–	–	1/15	6.7	3/204	1.5	0.273	1/15	6.7	7/204	3.4	0.535	1/15	6.7	8/204	3.9	0.597	9/15	60.0	115/204	56.4	0.799
Induration/fibrosis	0/15	–	0/204	–	–	0/15	–	0/204	–	–	0/15	–	1/204	0.5	0.931	0/15	–	1/204	0.5	0.931	3/15	20.0	6/204	2.9	**0.019**
Pruritus/itching	0/15	–	2/204	1.0	0.867	0/15	–	2/204	1.0	0.867	1/15	6.7	10/204	4.9	0.718	1/15	6.7	11/204	5.4	0.777	1/15	6.7	3/204	1.5	0.273
Desquamation	0/15	–	1/204	0.5	0.931	0/15	–	1/204	0.5	0.931	2/15	13.3	10/204	4.9	0.233	3/15	20.0	18/204	8.8	0.205	0/15	–	14/204	6.9	0.359
Rash: dermatitis	0/15	–	21/204	10.3	0.209	2/15	13.3	74/204	36.3	0.071	8/15	53.3	136/204	66.7	0.319	10/15	66.7	148/204	72.5	0.620	2/15	13.3	33/204	16.2	0.831
Teleangiectasia	0/15	–	0/204	–	–	0/15	–	0/204	–	–	0/15	–	0/204	–	–	0/15	–	0/204	–	–	0/15	–	0/204	–	–
Skin ulceration	0/15	–	0/204	–	–	0/15	–	0/204	–	–	0/15	–	0/204	–	–	0/15	–	2/204	1.0	0.867	0/15	–	0/204	–	–
Burn	0/15	–	0/204	–	–	0/15	–	0/204	–	–	0/15	–	1/204	0.5	0.931	0/15	–	3/204	1.5	0.807	0/15	–	1/204	0.5	0.931
Edema	1/15	6.7	16/204	7.8	0.957	2/15	13.3	16/204	7.8	0.468	2/15	13.3	17/204	8.3	0.510	4/15	26.7	20/204	9.8	0.081	3/15	20.0	20/204	9.8	0.256

Table 3 (continued)

	Toxicity at 5th day					Toxicity at 10th day					Toxicity at 16th day					Toxicity at 20th day					Toxicity at 1 month				
	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*
Nodes excised ≥ 10																									
No. of pts with toxicity	14/38	36.8	21/181	11.6	**0.0003**	21/38	55.3	63/181	34.8	**0.030**	30/38	78.9	125/181	69.1	0.307	32/38	84.2	134/181	74.0	0.261	31/38	81.6	123/181	68.0	0.140
Dry skin	0/38	–	0/181	–	–	0/38	–	1/181	0.6	0.826	0/38	–	1/181	0.6	0.826	1/38	2.6	1/181	0.6	0.347	2/38	5.3	6/181	3.3	0.562
Hyperpigmentation	0/38	–	0/181	–	–	2/38	5.3	2/181	1.1	0.157	3/38	7.9	5/181	2.8	0.177	2/38	5.3	7/181	3.9	0.674	25/38	65.8	100/181	55.2	0.311
Induration/fibrosis	0/38	–	0/181	–	–	0/38	–	0/181	–	–	0/38	–	1/181	0.6	0.826	0/38	–	1/181	0.6	0.826	1/38	2.6	8/181	4.4	0.691
Pruritus/itching	2/38	5.3	0/181	–	**0.029**	2/38	5.3	0/181	–	**0.029**	2/38	5.3	9/181	5.0	0.999	3/38	7.9	9/181	5.0	0.480	0/38	–	4/181	2.2	0.464
Desquamation	0/38	–	1/181	0.6	0.826	0/38	–	1/181	0.6	0.826	0/38	–	12/181	6.6	0.177	3/38	7.9	18/181	9.9	0.742	2/38	5.3	12/181	6.6	0.813
Rash: dermatitis	7/38	18.4	14/181	7.7	0.063	18/38	47.4	58/181	32.0	0.106	28/38	73.7	116/181	64.1	0.344	30/38	78.9	128/181	70.7	0.407	10/38	26.3	25/181	13.8	0.095
Teleangiectasia	0/38	–	0/181	–	–	0/38	–	0/181	–	–	0/38	–	0/181	–	–	0/38	–	0/181	–	–	0/38	–	0/181	–	–
Skin ulceration	0/38	–	0/181	–	–	0/38	–	0/181	–	–	0/38	–	1/181	0.6	0.826	1/38	2.6	1/181	0.6	0.347	0/38	–	0/181	–	–
Burn	0/38	–	0/181	–	–	0/38	–	0/181	–	–	0/38	–	0/181	–	–	2/38	5.3	1/181	0.6	0.083	1/38	2.6	0/181	–	0.174
Edema	9/38	23.7	8/181	4.4	**0.0006**	8/38	21.1	10/181	5.5	**0.006**	6/38	15.8	13/181	7.2	0.115	7/38	18.4	17/181	9.4	0.130	11/38	28.9	11/181	6.1	**0.0002**
HT																									
No. of pts with toxicity	26/172	15.1	9/47	19.1	0.657	64/172	37.2	20/47	42.6	0.618	119/172	69.2	35/47	74.5	0.601	129/172	75.0	36/47	76.6	0.973	117/172	68.0	36/47	76.6	0.339
Dry skin	0/172	–	0/47	–	–	1/172	0.6	0/47	–	0.785	1/172	0.6	0/47	–	0.785	2/172	1.2	0/47	–	0.616	4/172	2.3	4/47	8.5	0.079
Hyperpigmentation	0/172	–	0/47	–	–	3/172	1.7	1/47	2.1	0.824	6/172	3.5	2/47	4.3	0.775	7/172	4.1	2/47	4.3	0.910	94/172	54.7	29/47	61.7	0.486
Induration/fibrosis	0/172	–	0/47	–	–	0/172	–	0/47	–	–	1/172	0.6	0/47	–	0.785	1/172	0.6	0/47	–	0.785	7/172	4.1	2/47	4.3	0.910

Table 3 (continued)

	Toxicity at 5th day					Toxicity at 10th day					Toxicity at 16th day					Toxicity at 20th day					Toxicity at 1 month				
	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*
Pruritus/itching	2/172	1.2	0/47	–	0.616	2/172	1.2	0/47	–	0.616	9/172	5.2	2/47	4.3	0.841	11/172	6.4	1/47	2.1	0.278	4/172	2.3	0/47	–	0.378
Desquamation	0/172	–	1/47	2.1	0.215	1/172	0.6	0/47	–	0.785	10/172	5.8	2/47	4.3	0.731	17/172	9.9	4/47	8.5	0.814	11/172	6.4	3/47	6.4	0.999
Rash: dermatitis	16/172	9.3	5/47	10.6		57/172	33.1	19/47	40.4	0.449	109/172	63.4	34/47	72.3	0.331	122/172	70.9	35/47	74.5	0.768	28/172	16.3	6/47	12.8	0.717
Teleangiectasia	0/172	–	0/47	–	–	0/172	–	0/47	–	–	0/172	–	0/47	–	–	0/172	–	0/47	–	–	0/172	–	0/47	–	–
Skin ulceration	0/172	–	0/47	–	–	0/172	–	0/47	–	–	1/172	0.6	0/47	–	0.785	2/172	1.2	0/47	–	0.616	0/172	–	0/47	–	–
Burn	0/172	–	0/47	–	–	0/172	–	0/47	–	–	0/172	–	0/47	–	–	2/172	1.2	1/47	2.1	0.634	1/172	0.6	0/47	–	0.785
Edema	13/172	7.6	4/47	8.5	0.804	15/172	8.7	3/47	6.4	0.645	14/172	8.1	5/47	10.6	0.584	19/172	11.0	5/47	10.6	0.999	19/172	11.0	4/47	8.5	0.649
CHT																									
No. of pts with toxicity	12/46	26.1	23/173	13.3	**0.032**	22/46	47.8	62/173	35.8	0.188	34/46	73.9	121/173	69.9	0.731	38/46	82.6	128/173	74.0	0.308	33/46	71.7	120/173	69.4	0.896
Dry skin	0/46	–	0/173	–	–	0/46	–	1/173	0.6	0.790	0/46	–	1/173	0.6	0.790	0/46	–	2/173	1.2	0.623	0/46	–	8/173	4.6	0.146
Hyperpigmentation	0/46	–	0/173	–	–	2/46	4.3	2/173	1.2	0.225	2/46	4.3	6/173	3.5	0.999	2/46	4.3	7/173	4.0	0.884	28/46	60.9	95/173	54.9	0.578
Induration/fibrosis	0/46	–	0/173	–	–	0/46	–	0/173	–	–	0/46	–	1/173	0.6	0.790	0/46	–	1/173	0.6	0.790	3/46	6.5	6/173	3.5	0.382
Pruritus/itching	1/46	2.2	1/173	0.6	0.420	1/46	2.2	1/173	0.6	0.420	3/46	6.5	8/173	4.6	0.596	3/46	6.5	9/173	5.2	0.708	3/46	6.5	1/173	0.6	**0.032**
Desquamation	1/46	2.2	0/173	–	0.210	0/46	–	1/173	0.6	0.790	2/46	4.3	10/173	5.8	0.760	6/46	13.0	15/173	8.7	0.383	2/46	4.3	12/173	6.9	0.569
Rash: dermatitis	7/46	15.2	14/173	8.1	0.168	19/46	41.3	57/173	32.9	0.377	31/46	67.4	113/173	65.3	0.929	36/46	78.3	122/173	70.5	0.392	5/46	10.9	30/173	17.3	0.402
Teleangiectasia	0/46	–	0/173	–	–	0/46	–	0/173	–	–	0/46	–	0/173	–	–	0/46	–	0/173	–	–	0/46	–	0/173	–	–
Skin ulceration	0/46	–	0/173	–	–	0/46	–	0/173	–	–	0/46	–	1/173	0.6	0.790	1/46	2.2	1/173	0.6	0.420	0/46	–	0/173	–	–
Burn	0/46	–	0/173	–	–	0/46	–	0/173	–	–	0/46	–	0/173	–	–	2/46	4.3	1/173	0.6	0.121	0/46	–	1/173	0.6	0.790
Edema	5/46	10.9	12/173	6.9	0.390	6/46	13.0	12/173	6.9	0.206	6/46	13.0	13/173	7.5	0.259	8/46	17.4	16/173	9.2	0.192	8/46	17.4	14/173	8.1	0.083

Table 3 (continued)

	Toxicity at 5th day					Toxicity at 10th day					Toxicity at 16th day					Toxicity at 20th day					Toxicity at 1 month				
	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*	Yes	%	No	%	*p*
HB																									
No. of pts with toxicity	23/106	21.7	12/113	10.6	**0.04**	45/106	42.5	39/113	34.5	0.285	79/106	74.5	76/113	67.3	0.301	90/106	84.9	76/113	67.3	**0.004**	71/106	67.0	79/113	69.9	0.748
Dry skin	0/106	–	0/113	–	–	1/106	0.9	0/113	–	0.484	1/106	0.9	0/113	–	0.484	2/106	1.9	0/113	–	0.233	3/106	2.8	5/113	4.4	0.558
Hyperpigmentation	0/106	–	0/113	–	–	4/106	3.8	0/113	–	0.053	5/106	4.7	3/113	2.7	0.446	6/106	5.7	3/113	2.7	0.289	58/106	54.7	63/113	55.8	0.985
Induration/fibrosis	0/106	–	0/113	–	–	0/106	–	0/113	–	–	0/106	–	1/113	0.9	0.516	0/106	–	1/113	0.9	0.516	6/106	5.7	3/113	2.7	0.289
Pruritus/itching	2/106	1.9	0/113	–	0.233	2/106	1.9	0/113	–	0.233	5/106	4.7	6/113	5.3	0.999	6/106	5.7	6/113	5.3	0.999	2/106	1.9	2/113	1.8	0.951
Desquamation	1/106	0.9	0/113	–	0.484	0/106	–	1/113	0.9	0.516	6/106	5.7	6/113	5.3	0.999	15/106	14.2	6/113	5.3	**0.047**	5/106	4.7	9/113	8.0	0.345
Rash: dermatitis	12/106	11.3	9/113	8.0	0.411	38/106	35.8	38/113	33.6	0.839	72/106	67.9	72/113	63.7	0.608	86/106	81.1	72/113	63.7	**0.007**	14/106	13.2	20/113	17.7	0.465
Teleangiectasia	0/106	–	0/113	–	–	0/106	–	0/113	–	–	0/106	–	0/113	–	–	0/106	–	0/113	–	–	0/106	–	0/113	–	–
Skin ulceration	0/106	–	0/113	–	–	0/106	–	0/113	–	–	0/106	–	1/113	0.9	0.516	1/106	0.9	1/113	0.9	0.999	0/106	–	0/113	–	–
Burn	0/106	–	0/113	–	–	0/106	–	0/113	–	–	0/106	–	0/113	–	–	3/106	2.8	0/113	–	0.112	1/106	0.9	0/113	–	0.484
Edema	11/106	10.4	6/113	5.3	0.174	14/106	13.2	4/113	3.5	**0.018**	12/106	11.3	7/113	6.2	0.268	17/106	16.0	7/113	6.2	**0.035**	18/106	17.0	4/113	3.5	**0.002**

The bold is related to the significant results

N number, *pts* patients, *HB* hypofractionated boost, *HT* hormonal therapy, *CHT* chemotherapy

Table 4 Predictive factors for late skin and subcutaneous toxicity: univariate analysis

	Toxicity at 6 months					Toxicity at 12 months				
	Yes	%	No	%	*p*	Yes	%	No	%	*p*
Hypertension										
No. of pts with toxicity	39/92	42.4	48/127	37.8	0.585	22/92	23.9	24/127	18.9	0.464
Dry skin	2/92	2.2	2/127	1.6	0.761	0/92	–	3/127	2.4	0.193
Hyperpigmentation	16/92	17.4	21/127	16.5	0.999	12/92	13.0	6/127	4.7	**0.049**
Induration/fibrosis	12/92	13.0	18/127	14.2	0.967	6/92	6.5	8/127	6.3	0.999
Pruritus/itching	1/92	1.1	0/127	–	0.420	0/92	–	0/127	–	–
Desquamation	2/92	2.2	0/127	–	0.175	0/92	–	0/127	–	–
Rash: dermatitis	6/92	6.5	3/127	2.4	0.149	1/92	1.1	0/127	–	0.420
Teleangiectasia	0/92	–	0/127	–	–	0/92	–	0/127	–	–
Skin ulceration	1/92	1.1	0/127	–	0.420	0/92	–	0/127	–	–
Burn	0/92	–	0/127	–	–	0/92	–	0/127	–	–
Edema	14/92	15.2	25/127	19.7	0.500	12/92	13.0	17/127	13.4	0.999
Collagenopathies										
No. of pts with toxicity	2/4	50.0	85/215	39.5	0.695	0/4	–	46/215	21.4	0.386
Dry skin	0/4	–	4/215	1.9	0.928	0/4	–	3/215	1.4	0.946
Hyperpigmentation	0/4	–	37/215	17.2	0.474	0/4	–	17/215	7.9	0.722
Induration/fibrosis	1/4	25.0	29/215	13.5	0.539	0/4	–	14/215	6.5	0.766
Pruritus/itching	0/4	–	1/215	0.5	0.982	0/4	–	0/215	–	–
Desquamation	1/4	25.0	1/215	0.5	**0.036**	0/4	–	0/215	–	–
Rash: dermatitis	1/4	25.0	8/215	3.7	0.164	0/4	–	1/215	0.5	0.982
Teleangiectasia	0/4	–	0/215	–	–	0/4	–	0/215	–	–
Skin ulceration	0/4	–	0/215	–	–	0/4	–	0/215	–	–
Burn	0/4	–	0/215	–	–	0/4	–	0/215	–	–
Edema	1/4	25.0	38/215	17.7	0.693	0/4	–	29/215	13.5	0.564
Diabetes										
No. of pts with toxicity	3/15	20.0	84/204	41.2	0.111	4/15	26.7	42/204	20.6	0.573
Dry skin	1/15	6.7	3/204	1.5	0.273	0/15	–	3/204	1.5	0.807
Hyperpigmentation	2/15	13.3	35/204	17.2	0.761	2/15	13.3	16/204	7.8	0.468
Induration/fibrosis	3/15	20.0	27/204	13.2	0.470	2/15	13.3	13/204	6.4	0.346
Pruritus/itching	0/15	–	1/204	0.5	0.931	0/15	–	0/204	–	–
Desquamation	0/15	–	2/204	1.0	0.867	0/15	–	0/204	–	–
Rash: dermatitis	1/15	6.7	8/204	3.9	0.598	0/15	–	1/204	0.5	0.931
Teleangiectasia	0/15	–	0/204	–	–	0/15	–	0/204	–	–
Skin ulceration	0/15	–	1/204	0.5	0.931	0/15	—	0/204	–	–
Burn	0/15	–	0/204	–	–	0/15	–	0/204	–	–
Edema	4/15	26.7	35/204	17.2	0.372	2/15	13.3	27/204	13.2	0.936
Nodes excised ≥ 10										
No. of pts with toxicity	21/38	55.3	66/181	36.5	**0.048**	20/38	52.6	27/181	14.9	**<0.0001**
Dry skin	1/38	2.6	3/181	1.7	0.676	2/38	5.3	1/181	0.6	0.084
Hyperpigmentation	11/38	28.9	25/181	13.8	**0.041**	11/38	28.9	7/181	3.9	**<0.0001**
Induration/fibrosis	11/38	28.9	19/181	10.5	**0.006**	6/38	15.8	8/181	4.4	**0.023**
Pruritus/itching	0/38	–	1/181	0.6	0.826	0/38	–	0/181	–	–
Desquamation	0/38	–	2/181	1.1	0.682	0/38	–	0/181	–	–
Rash: dermatitis	3/38	7.9	6/181	3.3	0.242	2/38	5.3	0/181	–	**0.029**
Teleangiectasia	0/38	–	0/181	–	–	0/38	–	0/181	–	–
Skin ulceration	0/38	–	1/181	0.6	0.826	0/38	–	0/181	–	–
Burn	0/38	–	0/181	–	–	0/38	–	0/181	–	–
Edema	10/38	26.3	29/181	16.0	0.202	12/38	31.6	17/181	9.4	**0.0007**

Table 4 (continued)

	Toxicity at 6 months					Toxicity at 12 months				
	Yes	%	No	%	*p*	Yes	%	No	%	*p*
HT										
No. of pts with toxicity	69/172	40.1	17/47	36.2	0.747	40/172	23.3	6/47	12.8	0.173
Dry skin	5/172	2.9	0/47	–	0.295	1/172	0.6	1/47	2.1	0.429
Hyperpigmentation	26/172	15.1	9/47	19.1	0.657	13/172	7.6	4/47	8.5	0.804
Induration/fibrosis	28/172	16.3	2/47	4.3	0.059	13/172	7.6	1/47	2.1	0.185
Pruritus/itching	1/172	0.6	0/47	–	0.785	0/172	–	0/47	–	–
Desquamation	1/172	0.6	1/47	2.1	0.429	0/172	–	0/47	–	–
Rash: dermatitis	6/172	3.5	3/47	6.4	0.401	1/172	0.6	0/47	–	0.785
Teleangiectasia	0/172	–	0/47	–	–	0/172	–	0/47	–	–
Skin ulceration	1/172	0.6	0/47	–	0.785	0/172	–	0/47	–	–
Burn	0/172	–	0/47	–	–	0/172	–	0/47	–	–
Edema	35/172	20.3	4/47	8.5	0.096	27/172	15.7	2/47	4.3	0.071
CHT										
No. of pts with toxicity	26/46	56.5	62/173	35.8	**0.017**	12/46	26.1	34/173	19.7	0.454
Dry skin	0/46	–	4/173	2.3	0.386	2/46	4.3	1/173	0.6	0.121
Hyperpigmentation	20/46	43.5	18/173	10.4	**< 0.0001**	9/46	19.6	10/173	5.8	**0.008**
Induration/fibrosis	12/46	26.1	19/173	11.0	**0.018**	2/46	4.3	12/173	6.9	0.570
Pruritus/itching	1/46	2.2	0/173	–	0.210	0/46	–	0/173	–	–
Desquamation	1/46	2.2	1/173	0.6	0.420	0/46	–	0/173	–	–
Rash: dermatitis	3/46	6.5	6/173	3.5	0.427	0/46	–	1/173	0.6	0.790
Teleangiectasia	0/46	–	0/173	–	–	0/46	–	0/173	–	–
Skin ulceration	0/46	–	1/173	0.6	0.790	0/46	–	0/173	–	–
Burn	0/46	–	0/173	–	–	0/46	–	0/173	–	–
Edema	13/46	28.3	27/173	15.6	0.078	5/46	10.9	23/173	13.3	0.859
HB										
No. of pts with toxicity	48/106	45.3	38/113	33.6	0.104	27/106	25.5	18/113	15.9	0.114
Dry skin	3/106	2.8	1/113	0.9	0.340	1/106	0.9	2/113	1.8	0.660
Hyperpigmentation	25/106	23.6	12/113	10.6	**0.017**	10/106	9.4	8/113	7.1	0.698
Induration/fibrosis	21/106	19.8	9/113	8.0	**0.019**	10/106	9.4	5/113	4.4	0.231
Pruritus/itching	1/106	0.9	0/113	–	0.484	0/106	–	0/113	–	–
Desquamation	1/106	0.9	1/113	0.9	0.968	0/106	–	0/113	–	–
Rash: dermatitis	5/106	4.7	4/113	3.5	0.679	1/106	0.9	0/113	–	0.484
Teleangiectasia	0/106	–	0/113	–	–	0/106	–	0/113	–	–
Skin ulceration	0/106	–	1/113	0.9	0.516	0/106	–	0/113	–	–
Burn	0/106	–	0/113	–	–	0/106	–	0/113	–	–
Edema	20/106	18.9	19/113	16.8	0.825	16/106	15.1	12/113	10.6	0.430

The bold is related to the significant results

N number, *pts* patients, *HB* hypofractionated boost, *HT* hormonal therapy, *CHT* chemotherapy

Ciammella et al. [18], with a median follow-up of 34 months, analyzed data of 212 women treated with hypofractionated WBRT (40.05 Gy in 15 fractions), followed, only in 55 patients at high risk of relapse, by a boost dose of 9 Gy in 3 fractions. HB administration resulted correlated to acute, but, unlike our results, not to late skin toxicity. This study, unlike the other two, evaluated also patient related comorbidities (diabetes and hypertension), showing that diabetes was related to subcutaneous late toxicity.

De Santis et al. [19], with a median follow-up of 32 months, evaluated 537 patients treated with WBRT (42.4 Gy in 16 fractions), followed, in 144 patients at high risk of relapse, by a boost dose administered either with standard fractionation (16 Gy in 8 fractions) or with a hypofractionated schedule (10 Gy in 4 fractions). This study evaluated the impact of patient clinical characteristics, performed treatments and dose inhomogeneities on acute skin toxicity and late fibrosis, showing, unlike our study, that

Table 5 Acute toxicity: univariate and multivariate Cox regression analysis

Explanatory variables	HR	95.0% CI		*p*
		Lower	Upper	
Univariate				
Hypertension	0.911	0.683	1.216	0.528
Collagenopathies	1.273	0.406	3.989	0.679
Diabetes	0.884	0.513	1.524	0.658
Nodes excised ≥ 10	1.275	0.872	1.865	0.210
HT	0.893	0.632	1.261	0.519
CHT	1.283	0.911	1.808	0.154
HB	1.341	1.008	1.784	0.044
Multivariate				
HB	1.262	0.911	1.747	0.161
Nodes excised ≥ 10	1.126	0.753	1.685	0.562
CHT	1.105	0.754	1.621	0.608

The bold is related to the significant results

HR hazard ratio, *CI* confidence interval, *HB* hypofractionated boost, *HT* hormonal therapy, *CHT* chemotherapy

Table 6 Late toxicity: univariate and multivariate Cox regression analysis

Explanatory variables	HR	95.0% CI		*p*
		Lower	Upper	
Univariate				
Hypertension	1.259	0.845	1.876	0.257
Collagenopathies	1.152	0.284	4.675	0.843
Diabetes	0.713	0.290	1.754	0.462
Nodes excised ≥ 10	1.710	1.084	2.696	0.021
HT	1.090	0.660	1.800	0.737
CHT	1.666	1.078	2.574	0.022
HB	1.368	0.917	2.043	0.125
Multivariate				
HB	1.049	0.650	1.692	0.846
Nodes excised ≥ 10	1.493	0.909	2.453	0.113
CHT	1.455	0.875	2.417	0.148

The bold is related to the significant results

HR hazard ratio, *CI* confidence interval, *HB* hypofractionated boost, *HT* hormonal therapy, *CHT* chemotherapy

boost administration resulted significantly correlated at multivariate analysis with acute skin reactions.

Furthermore, De Santis et al. [20], in a second report, evaluated the association of hypofractionated WBRT (with or without a HB) with trastuzumab finding a safe profile in terms of acute skin and cardiac toxicity. In particular, HB had a significant impact on acute skin toxicity. In a recent paper the same authors [21], evaluated the same treatment schedule in elderly patients, showing it was effective and safe: once again HB resulted a risk factor for acute skin toxicity.

Comparing the present study with the prospective aforementioned studies, the major limitation of our series is that a longer follow-up is needed in order to better define late toxicity and that cosmesis was not recorded for all patients and therefore not analyzed. However, in our opinion, the present study, unlike the others described above, has the following strengths: the great number of toxicity related factors (patients related factors, treatment related factors and RT-treatment related volumes) analyzed, the strict check-up visit schedule used and the detailed univariate analysis that allow radiation oncologist to prevent and to promptly treat any kind of skin and subcutaneous toxicity based on patient and treatment related risk factors.

In conclusion, our data confirm that a moderate hypofractionated WBRT schedule, even followed by a HB, is safe and well tolerated, since no case of treatment interruption due to acute toxicity and no acute or late G3 toxicities occurred. Therefore, our results support the use of hypofractionated WBRT with a sequential HB in clinical practice, allowing to reduce treatment time, resource utilization, costs for healthcare provider, and waiting lists with a significant improvement in QoL of breast cancer patients. Longer follow-up is warranted to estimate late toxicity and treatment outcomes and to confirm our favorable results.

Compliance with ethical standards

Ethical standards The study was conducted in accordance with the Helsinki declaration as revised in 2000. Written informed consent was obtained from all patients.

Conflict of interest The authors declare no conflict of interest.

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