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Factors influencing acute and late toxicity in the era of adjuvant hypofractionated breast radiotherapy

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ABSTRACT

Purpose: To evaluate toxicity in breast cancer patients treated with anthracycline and taxane based chemotherapy and whole breast hypofractionated radiotherapy, and to identify the risk factors for toxicity.
Methods and materials: 537 early breast cancer patients receiving hypofractionated radiotherapy after conservative surgery were enrolled from April 2009 to December 2014, in an Italian cancer institute. The dose was 42.4 Gy in 16 daily fractions, 2.65 Gy per fraction. The boost to the tumor bed was administered only in grade III breast cancer patients and in patients with close or positive margins. Acute and late toxicity were prospectively assessed during and after radiotherapy according to RTOG scale. The impact of patients clinical characteristics, performed treatments and dose inhomogeneities on the occurrence of an higher level of acute skin toxicity and late fibrosis has been evaluated by univariate and multivariate analysis.
Results: The mean age was 74 (range 46–91 yrs). 27% of patients received boost. 22% of cases (n = 119) received also chemotherapy. The median follow-up was 32 months.
G1 and G2/G3 acute skin toxicity were 61.3% and 20.5% and G1 and G2/G3 late fibrosis 12.6% and 4.3% respectively.
Chemotherapy ($p = 0.04$), diabetes ($p = 0.04$) and boost administration ($p < 0.01$) were found to be statistically significant on the occurrence of late fibrosis, but a multivariate analysis did not show any factors connected. The boost administration ($p < 0.01$), the breast volume ($p = 0.05$), dose inhomogeneities ($p < 0.01$) and boost volume ($p = 0.04$) were found to be statistically significant as concerns the occurrence of acute skin reaction at the univariate analysis, but only the boost administration ($p = 0.02$), at multivariate analysis.
Conclusions: The results of our study, according to the large randomized trials, confirmed that hypofractionated whole breast irradiation is safe, and only the boost administration seems to be an important predictor for toxicity. Chemotherapy does not impact on acute and late skin toxicity.

Introduction

A recent systemic review of 17 randomized trial involving more than 10,000 patients confirmed the benefit of adjuvant radiotherapy on local control and overall survival for women with early breast cancer [1]. In Italy and in other countries such as United States, conventional 50 Gy in 25 fractions is most widely used schedule for whole breast irradiation (WBI). Shortened, hypofractionated schemes (HF-WBI) were compared to standard fractionation in many randomized trials and at a follow-up of 5- to 10-years equivalence in terms of local control, survival and toxicity has been shown [2–4]. The first randomized trial was conducted in

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Canada where a dose of 42.5 Gy in 16 fractions against 50 Gy in 25 fractions were compared, resulting in equivalent local control and breast cosmesis [2].

The two most recent randomized studies, conducted in UK, have demonstrated that hypofractionation offers a favorable tolerance and loco-regional tumor control [3,4]. Hypofractionation has important practical advantages and biological implications. Its convenience, also in terms of cost savings to the patient and the health care provider, may facilitate patients' acceptance and compliance with radiotherapy. As usual in clinical trials, patients enrolled are those satisfying restrictive inclusion criteria while in real clinical practice patients can have various other risk factors that can influence toxicity. For example the number of patients in the randomized trials who underwent adjuvant chemotherapy and hypofractionated radiotherapy was very low and only few studies have investigated this point. For this reason at the ASTRO consensus statement didn't reach agreement on hypofractionated radiotherapy in patients undergoing chemotherapy. Also at the recent St Gallen Consensus Conference a part of the Panel didn't accept hypofractionated regimen for patients with prior chemotherapy [5].

The aim of this prospective study was evaluate the toxicity and to investigate the impact of the risk factors along with other treatments (including chemotherapy), dosimetric variables, and comorbidities (mainly diabetes and hypertension) on the acute and late toxicity of hypofractionated radiotherapy for early breast cancer cases, in the real clinical practice of a unique Italian cancer institute.

Materials and methods

Patients, data collection and radiation treatment

Breast cancer patients receiving hypofractionated whole breast irradiation at National Cancer Institute in Milan from April 2009 to December 2014, were considered for the study. Inclusion criteria were: a) breast conservative surgery (quadrantectomy) before radiotherapy; b) early breast cancer cases: pathological stage pT1-pT2 and pN0-pN1 according to TNM stage [6]; c) systemic therapy prescribed after multidisciplinary evaluation; d) patients had to be at least 70 years old, but we also included younger patients who ask for a shorter treatment time because of social or economical reasons. So, in this cohort we enrolled 510 patients with age $\geq$70 years and 27 patients with age<70 years; e) follow up longer than 6 months. All patients underwent clinical examination both before irradiation and weekly during the treatment, after the course every six months. Before starting radiotherapy several clinical data including age, body mass index (BMI), diabetes, hypertension and information on medical treatments (type and adjuvant chemotherapy, hormonal deprivation, other concomitant drugs) were prospectively collected. Missing data on comorbidities as diabetes and hypertension were partially collected from the Institutional breast cancer registry [7]. The planning CT scan (5 mm slice thickness) from the level of the larynx to the upper abdomen was obtained in the supine position using “breast-board” or other personalized immobilization device with both arms raised above the head. CTV (Clinical Target Volume) and PTV (Planning Target Volume) were defined according to ESTRO guidelines [8]. Organs at risk (OARs), lungs and heart, were contoured. A three dimensional conformal radiotherapy was planned both for whole breast and boost irradiation. For the irradiation of the whole breast, two isocentric tangential fields were used and the plans were optimized by using wedge filter, bolus or the MLC. In general, two beams were used also for the boost irradiation. Whole breast was treated to a total dose of 42.4 Gy in 16 consecutive daily fractions, 2.65 Gy per fraction. The boost prescription followed a prospective prognostic factors policy based on previous published experience [2,9]. The boost dose was 10 Gy in 4 fractions for grade III invasive breast cancer and 16 Gy in 8 fractions for patients with close (<1 mm) or positive margins, if a re-excision of the tumor bed could not be performed.

The dose was prescribed to the ICRU reference point and the dosimetric objective was to cover 95% of the target volume with at least 95% of the prescribed total dose (PTD); in few cases of peculiar anatomical shape we accepted that 95% of the target volume receiving 90% of the PTD. For each patient, dose volume histograms (DVHs) for the PTV and OARs were obtained. Dosimetric data were also collected with special focus on dose inhomogeneity defined as the absolute volumes of breast tissues exposed to dose $\geq$44.52 Gy (105% of PTD), $\geq$45.37 Gy (107% of PTD) and $\geq$46.64 Gy (110% of PTD). Surveillance for disease recurrence included a clinical examination at every time point and bilateral mammography once a year. Acute skin toxicity was assessed during the treatment, at the end of radiotherapy, 15 days after the treatment and then every 6 months; while late effects were assessed every 6 months. Acute and late skin toxicity were evaluated in accordance with the RTOG grading scale. We considered for our analysis late fibrosis at the last follow up because there were no significative difference in terms of toxicity with the previous follow up.

Pathology

Breast Cancer (BC) was classified according to the histological type and the 2011 TNM classification of malignant tumors [6]. We also analyzed patients stratified by distinct subtypes: luminal A (ER positive and/or PgR positive, HER-2 negative, low Ki 67 < 19%); Luminal B HER2 negative (ER positive and/or PgR positive, HER-2 negative, high Ki 67); Luminal B HER2 positive (ER positive and/or PgR positive, HER-2 positive, any Ki 67); HER-2 overexpressing (ER negative, PgR negative and HER-2 positive); basal like or triple negative (ER negative, PgR negative and HER-2 negative, cytoker at in 5/6 positive and/or epidermal growth factor receptor positive) [5].

Statistical analysis

A descriptive statistical analysis was used with all the variables.

To investigate the impact of the clinical and pathological patients' characteristics along with dosimetric variables and comorbidities on the risk of developing an increment in the toxicity score, we estimated odds ratios for a shift in the direction of a worse outcome on toxicity score, according to the RTOG. These ratios were estimated with univariate ordinal logistic regression when the score toxicity was equal or higher than to G2, otherwise odds ratios were estimated with binomial logistic regression. The *chemotherapy* variable includes adjuvant and neo-adjuvant treatment. The *breast volume* (PTV) variable has been categorized in three homogeneous groups by tertiles. The breast volume medians, included in the three dose level selected (105, 107 and 110% of PTD), were used to split the distribution into 2 groups. Multivariate ordinal logistic regression analysis was performed in order to find predictive factors for acute skin radiation and late fibrosis toxicity. The model included variables resulting significant in the univariate analysis. All analyses were performed with STATA software [10].

Results

Cancer patients enrolled in the study were 537. After a median follow-up of 32 months the 96% of the patients was alive and disease-free. Patients' characteristics are shown in Table 1. The median age was 74 (range 46–91 years) with the 97% of patients older than 65 years. The BMI mean was 25.5 kg/m2. The 9% and 48%

was affected by diabetes and hypertension respectively. One hundred and nineteen patients received chemotherapy (3 cycles of Adriamicin 60 mg/m^2 and 3 cycles of Taxol 200 mg/m^2, then 3 cycles of CMF with Ciclofosfamide 600 mg/m^2, methotrexate 40 mg/m^2 and Fluorouracil 600 mg/m^2) [11]. Sixty-one patients (11.3%) underwent trastuzumab therapy and four hundred and forty-one (81.6%) hormonotherapy. The mean time between chemo and radiotherapy was about 2 months, with a range of 6 days–3.8 months. The boost was administered in 144 patients (27%). Invasive ductal carcinoma (CDI) was the most frequent histological type (78.3%) and the commonest subtype was the luminal A (45%). Dosimetric characteristics are reported in Table 2. The average breast volume was 722.1 cc (range 151.6–2776.6 cc) and the average boost volume was 54.1 cc (range 3.6–184.8 cc). Generally, with tangential fields technique the dose inhomogeneities are usually unavoidable and often significant. For each dose level selected (>105%, >107%, >110% of PTD) the breast volume encompassed were 149.7 cc (range 0–1074), 91.7 cc (range 0–897 cc) and 56.1 cc (range 0–700 cc) respectively. In Fig. 1 is depicted the positive Person correlation (r) between the volume enclosed by 105%, 107% and 110% of the prescription dose and the breast volume. Although the planning process allows to limit overdoses, the number of patients with a maximum dose less than 105%, 107% and 110% of the PD were 2, 6 and 88 respectively. Table 3 shows the frequency distribution of acute and late score toxicity. More than 20% of patients developed G2 or G3 acute skin toxicity and the 99.6% of them had no late skin toxicity. Severe acute asthenia (G2 toxicity score) was developed by the 2.3% of patients and late asthenia was no found in the 99.6%. Acute and late (>G2) edema was found in only 7 (1.3%) and 9 (1.7%) patients respectively. Acute and late (>G2) fibrosis was found respectively in 5 (0.9%) and 23 (4.3%) patients. Because of these results, the impact of the risk factors along with dosimetric variables and comorbidities was studied only for the acute skin toxicity and late fibrosis and it has been evaluated in univariate and multivariate analysis (Table 4, Table 5). No treatment interruption was necessary because of toxicity. The boost administration ($p < 0.01$), the breast volume ($p = 0.05$), dose inhomogeneities ($p < 0.01$) and boost volume ($p = 0.04$) were found to be statistically significant as concerns the occurrence of acute skin reaction at the univariate analysis. When we adjusted for age, breast volume and dose inhomogeneity, results suggests that only the boost administration is still significant. Other clinical factors such as diabetes or hypertension were not correlated with the development of acute skin reaction. Diabetes ($p = 0.04$), boost administration ($p < 0.01$), chemotherapy ($p = 0.04$) and dose inhomogeneity were found to be statistically significant on the occurrence of late fibrosis, but a multivariate analysis did not show any factors correlated to late fibrosis.

Table 1
Patient and tumor characteristics (537 early breast cancer cases) by chemotherapy.

Characteristics	Patients receiving chemotherapy N (%)	Patients not receiving chemotherapy N (%)y
Median age (range)	71 (63–87)	75 (46–91)
BMI mean (range)	25.5 (18.9–37.5)	26.1 (24.6–27.5)
Hypertension		
No	65 (54.6%)	216 (51.7%)
Yes	54 (45.4%)	202 (48.3%)
Diabetes		
No	106 (89.1%)	384 (91.9%)
Yes	13 (10.9%)	34 (8.1%)
Histological type		
CDI	56 (47.1%)	185 (44.3%)
CLI	14 (11.8%)	44 (10.5%)
CDI + CLI	6 (5%)	21 (5%)
Other	43 (36.1%)	168 (40.2%)
Breast side		
Right	60 (50.4%)	208 (49.8%)
Left	59 (49.6%)	210 (50.2%)
pT		
pT1	91 (76.5%)	373 (89.2%)
pT2	28 (23.5%)	45 (10.8%)
pN		
pN0-pN0(i+)	66 (55.5%)	300 (71.8%)
pN1	52 (43.7%)	51 (12.2%)
Unknown	1 (0.8%)	67 (16%)
Grading		
G1	2 (1.7%)	42 (10.5%)
G2	46 (38.7%)	304 (72.3%)
G3	71 (59.7%)	72 (17.2%)
Surgical margins		
Negative	111 (93.3%)	402 (96.2%)
Close (< 1 mm)	1 (0.8%)	4 (1%)
Close (> 1 mm and <2 mm)	6 (5.1%)	10 (2.4%)
Positive	1 (0.8%)	2 (0.5%)
ER[a]		
Positive	87 (73.1%)	400 (95.7%)
Negative	32 (26.9%)	18 (4.3%)
PGR[b]		
Positive	80 (67.2%)	374 (89.5%)
Negative	39 (32.8%)	44 (10.5%)
HER2[c]		
Positive	39 (32.8%)	22 (5.3%)
Negative	80 (67.2%)	396 (94.7%)
Ki67		
<20	15 (12.6%)	243 (58.1%)
>=20	100 (84%)	158 (37.8%)
Unknown	4 (3.4%)	17 (4.1%)
Subtype		
Luminal A	8 (6.7%)	231 (55.3%)
Luminal B HER2 neg	57 (47.9%)	150 (35.9%)
HER2 pos disease	37 (31.1%)	19 (4.6%)
Triple negative	16 (13.5%)	11 (2.6%)
Unknown	1 (0.8%)	7 (1.7%)
Hormonotherapy		
No	34 (28.6%)	64 (15.3%)
Yes	85 (71.4%)	354 (84.7%)
Boost administration		
No	58 (48.7%)	335 (80.1%)
Yes	61 (51.3%)	83 (19.9%)

[a] Estrogen receptor.
[b] Progesterone receptor.
[c] Her2 neu receptor.

Discussion

Three randomized trials in the last years have compared hypofractionated with conventional radiotherapy for whole breast irradiation. In the Canadian trial 1234 women with early-breast cancer were randomized after breast conserving surgery to HF-WBI (42.5 Gy/16 fx) or standard course (50 Gy/25 fx). This study demonstrated with a median follow up of 12 years comparable results between the two treatments in terms of local control and toxicity [2]. The UK standardization of breast radiotherapy (START) Trial A enrolled 2236 patients randomized to conventional radiation therapy versus two different schedules of hypofractionation (41.6 or 39 Gy in 13 fractions) [3]. In the START B trial, 2215 women with breast cancer were randomized after breast conserving surgery or mastectomy to standard irradiation (50 Gy/25 fx) or accelerated HF-WBI (40 Gy/15 fx) [4]. Both trials showed similar outcomes. Patient selection, length of follow-up, use of systemic therapy and radiation boost were slightly different in these three randomized trials. In the Canadian study no patient received boost irradiation and only 10.9% received adjuvant systemic therapy. In the START A and B Trials 22% and 35% of patients, respectively, received adjuvant chemotherapy and, although its use was not standardized, most patients received boost at the discretion of the treating physician or department policy. In our study we decided to give the boost to grade 3 tumor patients, for the increased risk of

Table 2
Dosimetric characteristics.

Characteristics	
Breast volume	
Average cc	722.1
Range	151.6–2776.6
Boost volume	
Average cc	54.1
Range	3.6–184.8
Breast volume receiving a dose ≥44.52 Gy (105% of PTD)	
Average cc	149.7
Range	0–1074
Breast volume receiving a dose ≥ 45.37 Gy (107% of PTD)	
Average cc	91.7
Range	0–897
Breast volume receiving a dose≥ 46.64 Gy (110% of PTD)	
Average cc	56.1
Range	0–700

Table 3
Frequency of score toxicity.

	Acute	Late
Skin toxicity		
0	98 (18.3%)	535 (99.6%)
1	329 (61.3%)	2 (0.4)
2	105 (19.6%)	
3	5 (0.9%)	
Asthenia		
0	370 (68.9%)	535 (99.6%)
1	151 (28.1%)	1 (0.2%)
2	16 (2.3%)	1 (0.2%)
Edema		
0	442 (82.3%)	482 (89.7%)
1	88 (16.4%)	46 (8.6%)
2	7 (1.3%)	8 (1.5%)
3		1 (0.2%)
Fibrosis		
0	471 (87.7%)	446 (83.1%)
1	61 (11.4%)	68 (12.6%)
2	5 (0.9%)	22 (4.1%)
3		1 (0.2%)

recurrence reported in the Canadian trial (2). Instead to patients with close (<1 mm) or positive margins the boost has been given in order to balance for inadequate surgery. The American Society of Therapeutic Radiology and Oncology (ASTRO) guidelines reported that the HF-WBI was appropriate in patients of 50 years or older at diagnosis, with pathological stage T1-T2 N0 disease treated with breast conserving surgery, without chemotherapy and with an inhomogeneity dose on radiation plan <7%. A consensus on the applicability of HF-WBI to young patients, boost and specially those underwent chemotherapy was not found for the lack of mature clinical data on these patient subsets. The addition of cytotoxic chemotherapy and hypofractionated radiation is supposed to increase the risk of acute toxicity and poor cosmetic outcome. The impact of the modern anthracycline- and taxane-based regimens in patients treated with HF-WBI is unknown. For this reason, the use of hypofractionated regimens has been cautiously implemented in patients also receiving chemotherapy. In a retrospective study, Hijal et al. [12] reviewed prospectively collected effects of HF-WBI (42.4 Gy in 16 fractions) in 162 patients. Forty-eight patients (30%) received chemotherapy. Rates of acute and late skin toxicity were not significantly different with or without the use of chemotherapy. Similarly, cosmetic outcomes were at least good in 71.8% of evaluable patients without chemotherapy and in 73.6% with chemotherapy. Although a similar proportion of patients had a fair or poor outcome in both study groups, the proportion of patients having an excellent outcome was higher in the no chemotherapy group, though the difference was non-significant (p 0.49). Kouloulias et al. [13] analyzed 116 patients treated with HF-WBI, of which 33 underwent adjuvant chemotherapy. Only at univariate analysis, chemotherapy contributed to the development of acute skin toxicity but with a critical value of 0.05. In our study we also evaluated the acute skin toxicity in both groups: patients receiving and not receiving chemotherapy but the analysis did not provide evidence of significant differences in score toxicity [14]. In the univariate and multivariate analysis chemotherapy was not correlated to acute skin toxicity, nevertheless our data showed a trend of acute skin toxicity ($p = 0.08$; OR = 1.5) in patients treated with chemotherapy. These findings may be related to the recall phenomena [15]. As in our study clinical and dosimetric factors have been also analyzed as predictors of toxicity for hypofractionated radiotherapy, Ciammella et al. [16] in another study found that breast volume ($p < 0.01$) and boost administration ($p = 0.05$) were correlated with acute skin toxicity, in 212 patients analyzed. Moreover age, hypertension and chemotherapy were not correlated with the development of acute skin reaction. In our study we found similar results. Furthermore, we found a significant association of the acute skin toxicity with inhomogeneities dose but when we adjusted for breast size and boost administration, there was no evidence that the risk of acute skin effects of radiotherapy was associated with that. Even though in Ciammella's study acute skin toxicity was no related to the dose inhomogeneity. At both univariate ($p < 0.01$) and multivariate analysis ($p = 0.019$) Ciammella found that only the boost administration was related to late skin toxicity but this result could not be confirmed in our study because we found that the 99.8% of cases have late skin toxicity score as 0. We also found, only at univariate analysis, that dose inhomogeneity and chemotherapy were associated with an increase of late fibrosis. However, in both studies the rate of moderate-high grade scores remained low. These data could be due to the short follow-up and

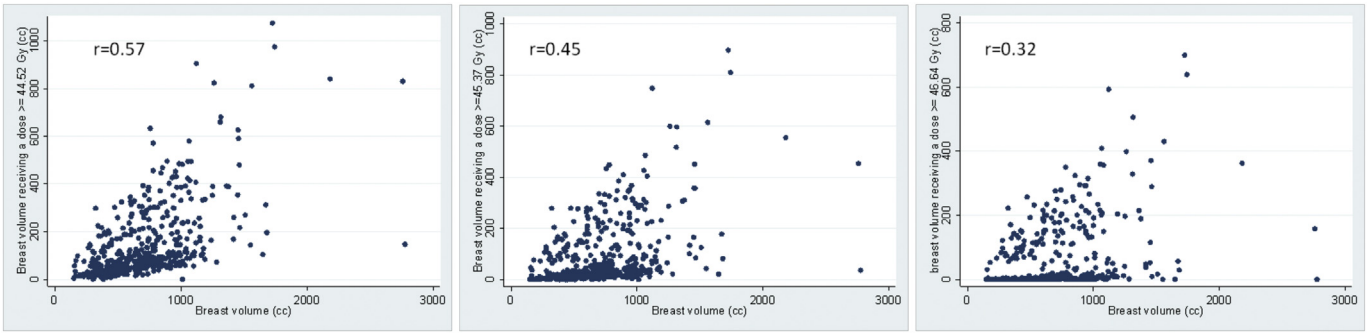

Fig. 1. Scatter-plot correlation of breast volume and dose inhomogeneities.

Table 4
Predictive factors for acute skin and late fibrosis radiation-induced toxicity: univariate analysis.

Variables	n	Univariate analysis			
		Acute skin toxicity		Late fibrosis toxicity	
		OR	p-value[a]	OR	p-value[a]
Diabetes					
No	490 (91.3%)	1		1	
Yes	47 (8.7%)	0.9	0.61	**2.0**	**0.04**
Hypertension					
No	281 (52.3%)	1		1	
Yes	256 (47.7%)	1.2	0.31	0.9	0.76
Chemotherapy					
No	418 (77.8%)	1		1	
Yes	119 (22.2%)	1.5	0.08	**1.7**	**0.04**
Hormonotherapy					
No	98 (18.3%)	1		1	
Yes	439 (81.7%)	1.1	0.57	0.9	0.88
Therapy					
No chemo no hormone therapy	64 (11.9%)	1		1	
Chemotherapy only	34 (6.3%)	2.2	0.06	1.5	0.43
Hormone therapy only	354 (65.9%)	1.4	0.19	1.0	0.98
Chemo and hormone therapy	85 (15.8%)	1.9	0.06	1.7	0.20
Breast volume (PTV)					
1°t (<553.1 cc)	149 (33%)	1		1	
2°t (553.1 − 806.9 cc)	151 (33.5%)	1.0	0.93	1.2	0.55
3°t (>806.9 cc)	151 (33.5%)	**1.6**	**0.05**	1.4	0.22
Breast PTV receiving a dose ≥44.52 Gy (105% of PTD)					
<Median value (92.5 cc)	220 (48.4%)	1		1	
>= Median value	235 (51.6%)	**2.0**	**<0.01**	**1.9**	**0.01**
Breast PTV receiving a dose ≥45.37 Gy (107% of PTD)					
<Median value (34.4 cc)	224 (48.7%)	1		1	
>= Median value	236 (51.3%)	**1.9**	**<0.01**	**2.0**	**<0.01**
Breast PTV receiving a dose ≥46.64 Gy (110% of PTD)					
<Median value (4.8 cc)	222 (48.3%)	1		1	
>= Median value	238 (51.7%)	**2.1**	**<0.01**	**1.6**	**0.04**
Boost administration					
No	393 (73.2%)	1		1	
Yes	144 (26.8%)	**2.5**	**<0.01**	**2.2**	**<0.01**
Boost volume					
<Median value (46.3)	63 (50.8%)	1		1	
>= Median value	61 (49.2%)	**2.1**	**0.04**	1.4	0.38

The bold is related to the significant results.
[a] Ordinal logistic regression p-value.

Table 5
Predictive factors for acute skin and late fibrosis radiation-induced toxicity: multivariate analysis.

Variables	n	Multivariate analysis			
		Acute skin toxicity		Late fibrosis toxicity	
		OR	p-value[a]	OR	p-value[a]
Diabetes					
No	490 (91.3%)			1	
Yes	47 (8.7%)			1.2	0.52
Chemotherapy					
No	418 (77.8%)			1	
Yes	119 (22.2%)			1.4	0.26
Breast volume (PTV)					
1°t (<553.1 cc)	149 (33%)	1		1	
2°t (553.1 − 806.9 cc)	151 (33.5%)	0.9	0.67	1.2	0.65
3°t (>806.9 cc)	151 (33.5%)	1.3	0.40	1.2	0.53
Breast PTV receiving a dose ≥44.52 Gy (105% of PTD)					
<Median value (92.5 cc)	220 (48.4%)	1		1	
>= Median value	235 (51.6%)	1.3	0.47	0.9	0.86
Breast PTV receiving a dose ≥45.37 Gy (107% of PTD)					
<Median value (34.4 cc)	224 (48.7%)	1		1	
>= Median value	236 (51.3%)	0.7	0.38	2.1	0.21
Breast PTV receiving a dose ≥ 46.64 Gy (110% of PTD)					
<Median value (4.8 cc)	222 (48.3%)	1		1	
>= Median value	238 (51.7%)	1.7	0.10	0.6	0.35
Boost administration					
No	393 (73.2%)	1		1	
Yes	144 (26.8%)	**1.9**	**0.02**	1.5	0.24

The bold is related to the significant results.
[a] Ordinal logistic regression p-value.

to the low boost dose (10 Gy) delivered in our study where only 8 patients were given 16 Gy. In fact The EORTC 22881-10882 trial [18] showed that fibrosis increases over a long period of time, so this result could be affected from the short follow up. Diabetes was found significant at univariate analysis on the occurrence of late fibrosis. This is not new to literature, in fact there are many published studies documenting late effects of radiation therapy for patients with diabetes mellitus because of microvessels pathology [17].

Conclusions

The results of our study, according to the large randomized trials, confirmed that HF-WBI is feasible and safe, because of the low rate of moderate-high scores toxicity. Chemotherapy didn't impact on acute skin toxicity but only on late fibrosis at univariate analysis, with a low percentage of G2-G3 fibrosis. Our study confirmed an increase of acute and late toxicity in patients who received additional boost. The recent Bartelink's data [19] showed that boost can be avoided in patients older than 60 because the very low benefit in local control is counterbalanced by a higher risk of moderate and severe fibrosis as showed in our study. Probably in order to give a more tailored therapy the extra radiation dose can be carefully considered in this setting of patients. A new study, with a longer follow-up, is ongoing at our Institution to confirm this point.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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