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Original Article

Quality assurance program and early toxicities in the phase III BONBIS randomized trial evaluating the role of a localized radiation boost in ductal carcinoma *in situ*

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ABSTRACT

Purpose: To describe the quality assurance (QA) program and early toxicities in the phase III randomized trial BONBIS (*NCT00907868*) on the role of a localized radiation boost in ductal carcinoma *in situ* (DCIS).
Materials and methods: From November 2008 to July 2014, 2004 patients were randomized in arm A (only whole breast radiotherapy, WBRT) and arm B (WBRT + boost). The QA program involved 44 participant centers that performed the dummy run (DR). Compliance and uniformity of clinical target volume (CTV) delineations, and dose prescription and delivery according to the BONBIS trial radiotherapy guidelines were analyzed. Acute toxicities (during and up to 3 months after radiotherapy completion, NCI-CTCAE v3.0 classification) were evaluated in 1929 patients.
Results: The differences in whole breast CTV (CTV1) and planning target volume (PTV1) were $\leq$10%, and the differences in boost CTV (CTV2) and PTV (PTV2) were $\geq$20% compared with the reference DR values; 95% of the prescribed dose encompassed 98.7% and 100% of the median CTV1 and CTV2. Grade $\geq$2 breast erythema (38.3% vs. 22.4% of grade 2 and 5.4% vs. 2.1% of grade 3, $p < 0.001$), grade $\geq$2 dermatitis (2.8% vs. 0.7%, $p < 0.001$), and grade 2 hyperpigmentation (6.9% vs. 3.6%, $p = 0.005$) were more frequent in arm B than arm A. No acute lung or cardiac toxicity was observed. Smoking history, large breast size, and large breast CTV were strong predictive factors of grade $\geq$2 acute skin toxicities.
Conclusions: The QA program showed deviations in breast and tumor bed delineation. The boost significantly increased acute skin toxicities.
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Mastectomy and breast conserving surgery (BCS) followed by whole breast radiotherapy (WBRT) are the standard therapeutic options for patients with ductal carcinoma in situ (DCIS), although no randomized clinical trial has compared these two strategies. Adjuvant WBRT, in which 50 Gy are delivered in 25 fractions over 5 weeks after BCS, significantly increases the local control rate with low toxicity incidence [1,2]. After the European Organization for

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Research and Treatment of Cancer (EORTC) trial results, a radiotherapy boost is standard practice in patients with invasive breast cancer after BCS. Currently, the role of an additional boost to the tumor bed in DCIS is assessed in two prospective trials (BONBIS trial – NCT00907868; and TROG trial – NCT00470236) that closed the patient inclusion phase in 2014. The final results on cancer outcome have not been published yet. The BONBIS study is a French multicenter prospective phase 3 randomized trial to evaluate the role of a 16 Gy-boost to the tumor bed in patients with DCIS after BCS and WBRT [3]. The primary objective is to compare the local recurrence-free survival after WBRT alone (standard treatment arm - ARM A) and after WBRT plus radiation boost (experimental arm – ARM B). To ensure that the results will not be compromised by inadequate techniques, a quality assurance (QA) procedure at each center was mandatory before the first patient inclusion.

Here, we present the results of the dummy run (DR) and compliance to the BONBIS trial radiotherapy guidelines by the participating centers, as well as the acute toxicities recorded in both arms.

Materials and methods

Patients

From November 2008 to July 2014, 2004 patients with DCIS were randomized according to a 1:1 ratio in arm A (n = 1002; no boost, standard arm) and in arm B (n = 1002; 16-Gy localized boost, experimental arm) (Fig. 1). Randomization was stratified by center, age (<40 years, ≥40 years), endocrine therapy (yes/no), histological grade (low vs intermediate vs high), initial presentation (clinical vs radiological) and margins (1–2 mm vs 3 mm).

Inclusion criteria were: 18-year-old patients with ECOG ≤2; DCIS without any infiltration component and no palpable axillary node; bilateral mammography performed in the last 6 months; and BCS with negative surgical margins (≥1 mm). Sentinel node biopsy was done to assess the node status in patients with high-grade DCIS. WBRT was started within 12 weeks following the last breast surgical procedure.

Exclusion criteria were: multicentric disease; positive sentinel node; ipsilateral local relapse; history of contralateral breast DCIS or invasive carcinoma; previous or concomitant other (non-breast cancer) malignant disease within the past 5 years, with the exception of adequately treated basal or squamous-cell carcinoma of the skin or in-situ carcinoma of the cervix; other non-malignant systemic diseases that would prevent extended follow-up; HIV positivity.

The protocol was approved by all local institutional review boards and by the independent ethics committee of Montpellier University. A written informed consent was signed by all patients. The BONBIS trial is registered at ClinicalTrials.gov, number NCT00907868.

Dummy run (DR)

Participant centers performed a DR procedure for radiation therapy QA before patient inclusion.

Two patients with breast cancer (BCpt1 and BCpt2) underwent 3D computed tomography (CT) imaging without contrast enhancement in free-breathing conditions (slice thickness = 5 mm at most) in the treatment conditions. The acquired CT images (from 2 cm upper the shoulder skin to 4 cm below the infra-mammary fold) were used for the DR. The CT data of these two patients, the proto-

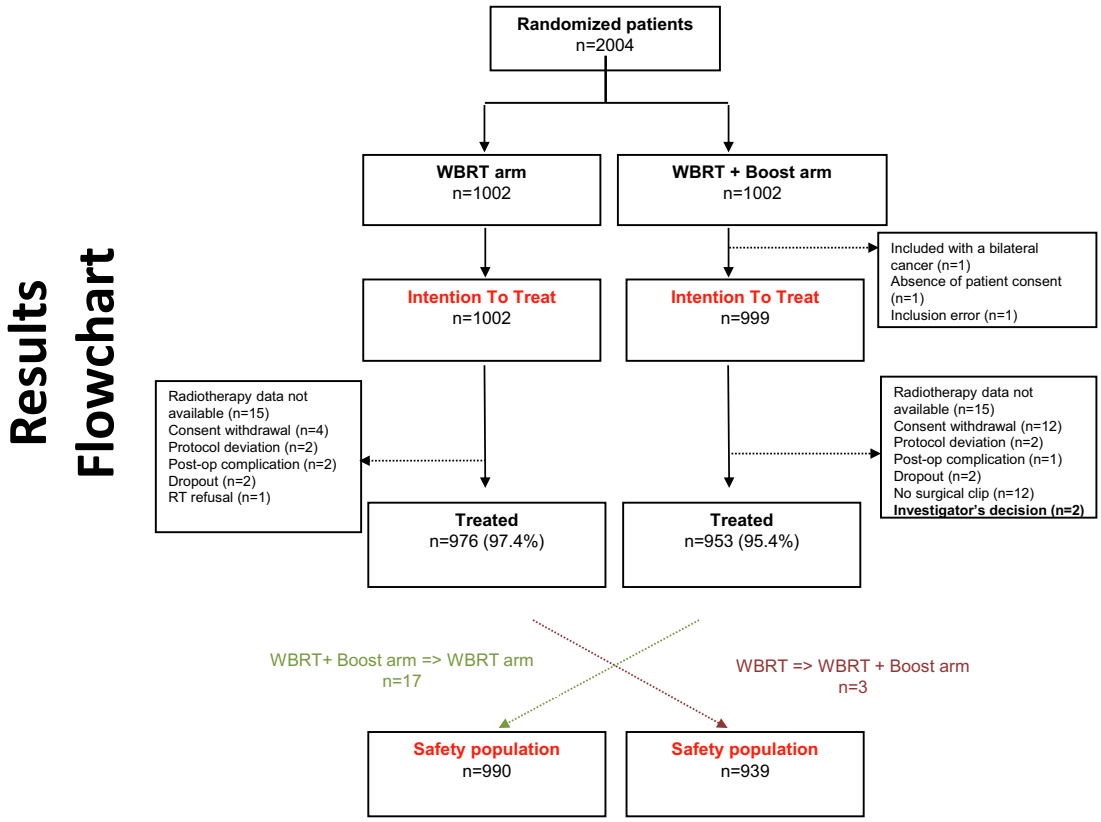

Fig. 1. BONBIS trial flowchart. The safety population of arm A included 17 patients from arm B who did not receive the boost, whereas the safety population of arm B included 3 patients from arm A who received the boost.

col guidelines for treatment planning (TP), and the dosimetric report forms (CRF) (*Supplementary Materials and Methods*) were sent to all investigators. At each center, the investigator delineated the clinical target volumes (breast clinical target volume, CTV1; boost clinical target volume, CTV2) on the BCpt1 and BCpt2 CT images, and then approved the TP according to the protocol guidelines. Then, he/she sent the finalized DR data (CRF and related TP) in DICOM format to the expert center. These data were imported in the Eclipse workstation for comparison with the reference TP (volumes and dose distribution) obtained by the expert center. The expert panel included three active radiation oncologists from the French Breast Cancer Society.

Volume differences between the investigators and expert panel CTVs were expressed in percentage: a difference of 10% for CTV1 and of 20% for CTV2 was considered clinically relevant. TP quality was assessed by checking that the mean and median CTV1 and CTV2 received 95% of the prescribed dose (V95%), and that the prescribed dose covered 95% of the CTV1 and the CTV2 (D95%).

Treatment procedures and toxicity evaluation

Radiotherapy was always delivered in supine position (arms up above the head) to ensure reproducibility during the simulation and treatment sessions. Target volumes and organs at risk are defined in *Supplementary Materials and Methods*. The irradiation fields were defined using a CT simulator. Only photons were allowed for WBRT, and at each center, radiotherapy had to be homogeneous and reproducible among patients. In arm A, a median dose to the target volume of 50 Gy in 25 fractions over 5 weeks was recommended, according to the International Commission on Radiation Units and Measurements report number 62 (3D-conformal radiotherapy) [4]. For patients with large breast volume, 20% of the total dose was given using 18 MV photons and 80% using 6 MV photons to avoid large hotspot areas. The dose to the whole breast was delivered by two opposed tangential fields. Each field was treated every day. To optimize the dose distribution, wedge filters were used if necessary. In arm B, patients received WBRT as in arm A, and an additional photon, electron or mixed photon-electron boost of 2 Gy per fraction, up to 16 Gy. On-line portal imaging to verify the treatment precision was required every day for the first 3 days, and then at least once per week for the treatment duration. Field adjustments were made when necessary.

Adjuvant endocrine therapy was administered at the investigators' discretion.

The primary endpoint was the local relapse-free survival that will be reported when 137 events will be registered during the follow-up. One of secondary endpoints was acute (i.e. within the first 3 months after radiotherapy initiation) cutaneous (erythema, ulceration, hyperpigmentation), lung and cardiac toxicities that were prospectively assessed and graded according to the Common Toxicity Criteria (CTC), version 3.0 [5]. All events were reported and defined at occurrence. Patients were monitored every week during radiotherapy, then at month 3 and 6, and every 6 months for 10 years.

Statistical analyses

The hypothesis of the primary endpoint (4% of local recurrence as a first event in the boost arm vs 7% in the arm without a boost) needed the inclusion of 1950 patients in total. Therefore, 2004 patients were enrolled to take into account potential inclusion mistakes and patients lost to follow-up.

Baseline characteristics and treatments were analyzed on an intention-to-treat basis according to the treatment arm allocated by randomization. Acute toxicities were analyzed in function of the treatment arm.

For the toxicity and DR analyses, continuous variables were described using medians, ranges and interquartile ranges, and compared with the Kruskal–Wallis or paired *t*-test. For categorical variables, frequencies and percentages were computed and compared with the chi-square or Fisher's exact test. Known risk factors of radiation-induced breast acute toxicities were analyzed using a logistic regression model: age, body mass index (BMI), breast size, clinical history (smoking, hypertension, diabetes, hormone replacement therapy), and also TP parameters (boost dose, boost technique, CTV1, and CTV2). Possible associations between parameters were investigated. Clinically relevant factors or variables with *p*-values <0.20 were included in the multivariate model with variables selected in ascending or descending order. All reported *p*-values were two-sided and were considered significant at the 5% level. All statistical analyses were performed using STATA 16.0 (StataCorp).

Results

Among the 53 participating centers, 45 performed the DR (including the expert center). In the 8 remaining centers, patients' accrual varied from 0.1% to 2% of the whole study population. However, CRF and DICOM data of 41/44 centers could be analyzed. The other centers failed to delineate either CTV1 or CTV2, or their DICOM data were not compatible with expert TPS, and consequently their data were considered as not available.

Analysis of the CTV1 and CTV2 delineated by the 41 participating centers showed that the median (range) CTV1 values were 783 mm^3 (214–996) and 975 mm^3 (252–1489) for BCpt1 and BCpt2, respectively (Fig. 2A and B). These volumes were smaller than those obtained by the expert panel in 25/41 centers for BCpt1 and in 25/41 centers for BCpt2 (Fig. 2Aa). CTV1 deviations were due to confusion between the definition of CTV1 and CTV2 (Fig. 2Ab), inclusion of the pectoral muscle in CTV1 (Fig. 2Ac), CTV1 delineation according to the tangent beam (Fig. 2Ad), and not consideration of the wires for the clinical definition of the mammary gland (Fig. 2Ae). The median (range) CTV1_*eval* (i.e. CTV1 minus a margin of 5 mm under the skin) values were 718 mm^3 (551–1037) and 837 mm^3 (388–1253) for BCpt1 and BCpt2, respectively. The median (range) PT volume (PTV1) values were 1158 mm^3 (832–1460) and 1354 mm^3 (647–2444) for BCpt1 and BCpt2, respectively, and were smaller than the reference values because CTV1 was often smaller than the reference value. The median (range) CTV2_*eval* values were 28 mm^3 (5–110) and 14 mm^3 (1–101) for BCpt1 and BCpt2, respectively (Fig. 2Ba), and they were mostly bigger than the reference values (in 19/40 centers for BCpt1 and in 24/41 centers for BCpt2). CTV2 deviations were explained by non-observance of the protocol guidelines: absence of surgical clip delineation (Fig. 2Bb), absence of the 15 mm-expansion from the surgical clips (hand-driven delineation, Fig. 2Bb), and missing surgical clips. As the CTV2 values were larger than the reference value, the PTV2 values also were larger than the reference value ($p < 0.001$). The median (range) PTV2 were 65.6 mm^3 (18.6–186.7) and 41 mm^3 (12–165) for BCpt1 and BCpt2, respectively.

Analysis of the dose distribution evaluation highlighted differences in CTV1_*eval* and CTV2_*eval* coverage and lung exposure between the investigators and the expert panel (Fig. 2C). The V95% for CTV1_*eval* ranged from 85 to 100% (95% CI: 92–100) and from 82 to 100% (95% CI: 89–100) (Fig. 2C, left panels), and the median values were 98.7% and 98% for BCpt1 and BCpt2, respectively. Similarly, the V95% of CTV2_*eval* ranged from 88 to

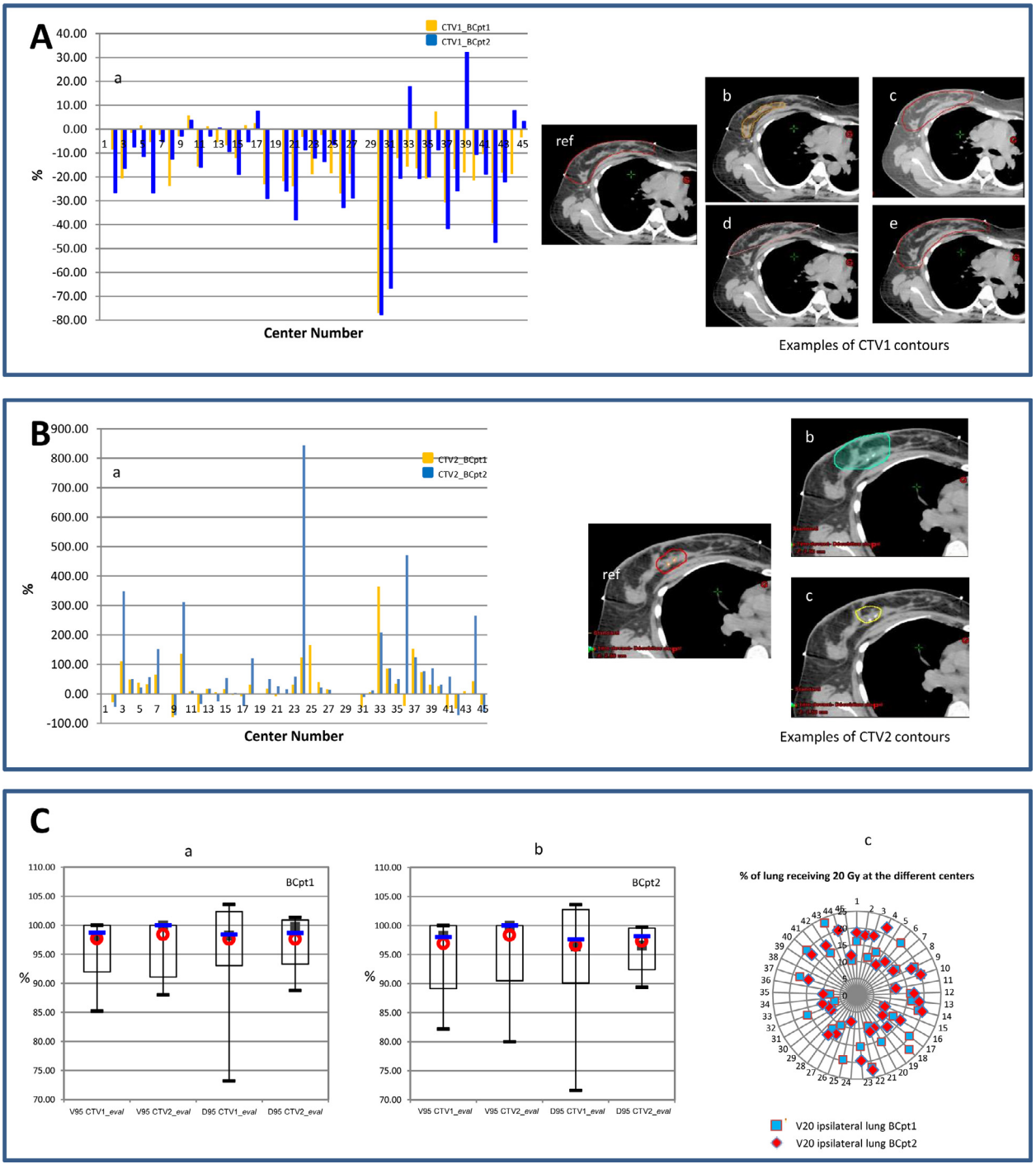

Fig. 2. (A – *a*) The *x*-axis shows the centers that performed the dummy run (#1: reference center; from #2 to #45: participating centers); data from centers #*x,y,z* could not be analyzed. The *y*-axis shows the differences (in percentage) between the CTV1 values obtained by the investigators and the expert panel (reference); *b–e*: Examples of errors in CTV1 delineation on CT images compared with the reference (ref). (B – *a*) The *x*-axis shows the centers that performed the dummy run (#1: reference center; from #2 to #45: participating centers); data from centers #*x,y,z* could not be analyzed. The *y*-axis shows the differences (in percentage) between the CTV2 values obtained by the investigators and the expert panel (reference); (*b and c*) Examples of errors in CTV2 delineation compared with the reference (ref). (C – *a and b*) Boxplots showing the results of the dummy run by the 44 participating centers (data from centers #*x,y,z* could not be analyzed): V95% and D95% for CTV1_*eval* and CTV2_*eval* in BCpt1 (a) and BCpt2 (b); the *y*-axis shows the values (in percentage) of V95% and D95%. Black square, reference value obtained by the expert panel; red circle, mean value of all analyzed treatment plans; blue line, median value of all analyzed treatment plans; whiskers, maximum and minimal value; upper and lower sides of the box, 95th and 5th percentiles. (*c*) Ipsilateral lung volume encompassed by the isodose of 20 Gy (V20) that should be smaller than 20% for BCpt1 (blue squares) and BCpt2 (red diamonds); the numbers (1–45) indicate the centers that performed the dummy run, each circle represents a V20 value (from 5 to 25%).

100% (95% CI: 90–100) and from 80 to 100% (95% CI: 90–100), and the median values were 100% for both BCpt1 and BCpt2.

The D95% for CTV1_*eval* ranged from 73 to 104% (95% CI: 93–102) and from 72 to 104% (95% CI:90–103) for BCpt1 and BCpt2, respectively. The D95% for CTV2_*eval* ranged from 89 to 101% (95% CI: 92–101) and from 89 to 100% (95% CI: 92–99.5) for BCpt1 and BCpt2, respectively (Fig. 2C, left panels).

The ipsilateral lung volume encompassed by the isodose of 20 Gy was >20% for BCpt1 and BCpt2 at three and two centers, respectively (Fig. 2C, right panel).

The baseline clinical characteristics of the included patients (intention-to-treat analysis; Fig. 1) were similar between arms (Table 1). Two-thirds of patients were postmenopausal, 55.1% had normal BMI, and 58% had large breast size (defined as bra/band size >90 and/or cup size >C). Nearly 70% of women were non-smoker, 25% had hypertension, and 5% had diabetes mellitus.

WBRT was performed in more than 95% of patients in both arms among whom 99.3% received the total dose of 50 Gy/25 fractions.

Table 1
Clinical baseline characteristics and radiotherapy parameters.

		ARM A (WBRT) n = 1002		ARM B (WBRT + BOOST) n = 999		TOTAL n = 2001		p-value
		N	%	*N*	%	*N*	%	
ECOG								0.872
	0	933	94.3	929	94.3	1862	94.3	
	1	48	4.9	50	5.1	98	5.0	
	2	8	0.8	6	0.6	14	0.7	
	Missing	*13*		*14*		*27*		
Hormonal status								0.974
	Premenopausal	312	31.4	311	31.4	623	31.4	
	Postmenopausal	680	68.6	680	68.6	1360	68.6	
	Missing	*10*		*8*		*18*		
BMI (kg/m^2)								0.213
	Underweight	26	2.8	21	2.3	47	2.5	
	Normal	510	55.0	512	55.1	1022	55.1	
	Overweight ≥25	232	25.0	262	28.2	494	26.6	
	Obesity (≥30)	159	17.2	134	14.4	293	15.8	
	Missing	*75*		*70*		*145*		
Breast size (bra and/or cup)								0.855
	Small	328	42.1	332	42.6	660	42.3	
	Large*	451	57.9	448	57.4	899	57.7	
	Missing	*223*		*219*		*442*		
Smoking habits								0.647
	Non-smoker	667	68.5	660	67.1	1327	67.8	
	Active smoker	138	14.2	154	15.7	292	14.9	
	History of smoking	169	17.3	169	17.2	338	17.3	
	Missing	*28*		*16*		*44*		
Hormone replacement therapy								0.639
	No	779	78.4	768	77.5	1547	77.9	
	Yes	215	21.6	223	22.5	438	22.1	
	Missing	*8*		*8*		*16*		
Hypertension								0.492
	Absent	747	74.6	758	75.9	1505	75.3	
	Present	254	25.4	240	24.1	494	24.7	
	Missing	*1*		*1*		*2*		
Diabetes mellitus								0.844
	Absent	950	95.0	950	95.2	1900	95.1	
	Present	50	5.0	48	4.8	98	4.9	
	Missing	*2*		*1*		*3*		
Adjuvant endocrine therapy								0.906
	Yes	50	5.1	48	5.0	98	5.0	
	No	930	94.9	915	95.0	1845	95.0	
	Missing	*22*		*36*		*58*		
WBRT	Yes	976	97.4	953	95.4	1929	96.4	
	No	26	2.6	46	4.6	72	3.6	
Total dose (WBRT)	Median [min;max]	50.0	[28;50]	50.0	[14;52]	50.0	[14;52]	
	IQR		48–50		46–50		40–50	
Boost to tumor bed (16 Gy in 8 fractions)	Yes	3	0.3	935	98.2	938	48.7	
	No	972	99.7	17	1.8	989	51.3	
	Missing	*27*		*47*		*74*		
Total dose (boost)	Median [min;max]	16.0	[16;16]	16.0	[2;18]	16.0	[2;18]	
	IQR		NA		8–16		8–16	
Boost technique	Photon	1	33.3	528	56.5	529	56.5	
	Electron	2	66.7	317	34.0	319	34.0	
	Mix	0		89	9.5	89	9.5	
	Missing	*999*		*65*		*1064*		
CTV1 (cm^3)	Median [min;max]	552.5	[13;2818]	537.0	[6;2747]	545.0	[6;2818]	
	IQR		352–862		337–839		345–844	
CTV2 (cm^3)	Median [min;max]	25.5	[9;77]	25.0	[0;754]	25.0	[0;754]	
	IQR		14–55		16–38		16–38	

WBRT: Whole-breast radiotherapy; BMI: Body mass index. *Large breast size was defined bra/band size >90 and/or cup size >C IQR = Inter Quartile Range.

In arm B, 98.2% of treated patients received at least one fraction of boost to the tumor bed, and 98.5% of them received the total dose of 16 Gy in 8 fractions using photons (56.5%), electrons (34%), or both (9.5%).

Acute toxicities could be evaluated in 990 (98.8%) and 939 (93.7%) patients in arm A and arm B. The reasons of exclusion are detailed in Fig. 1. The localized boost significantly increased the rate of grade ≥2 breast erythema (38.3% vs. 22.4% of grade 2; and 5.4.1% vs. 2.1% of grade 3 in arms B and A, respectively; $p < 0.001$), grade ≥2 dermatitis ($p < 0.001$), and grade 2 hyperpigmentation ($p = 0.005$). No acute lung or cardiac toxicity was observed (Table 2).

Overall, grade ≥2 acute skin toxicity was reported by 39.5% of patients. In univariate analysis (Table 3), grade ≥2 acute skin toxicity events were significantly associated ($p < 0.001$) with large breast size, BMI ≥25, diabetes, and hypertension ($p = 0.01$), but not with smoking. Electron boost significantly decreased the risk of grade ≥2 skin toxicities ($p < 0.001$). Conversely, grade ≥2 skin toxicities were significantly associated with large CTV1 (>500 cm^3) and CTV2 (>25 cm^3) ($p < 0.001$). In multivariate analysis (Table 4), active smoker or history of smoking, boost addition and large CTV1 (>500 cm^3) significantly increased the risk of grade ≥2 acute skin toxicities.

Discussion

As the primary endpoint of the BONBIS trial was the local relapse-free survival, a QA procedure was required to ensure that radiotherapy was correctly delivered. More than 80% of the participant centers took part in the QA program. Overall, analysis of the requested data (provided only by 41 of the 53 participating centers) showed deviations in the delineated volumes. Previous studies reported inter-observer variations in breast planning target volume delineation [6,7]. The recent QA of the randomized Skagen Trial 1 reported a low rate of inter-observer variability in contouring (target volume and organs at risks) [8]. As inter-observer variability is smaller when the palpable glandular breast tissue is marked with a lead wire before CT imaging [9], radio-opaque markers were placed in the breast of the two patients to ensure inter-observer reproducibility in the BONBIS QA. Nevertheless, some BONBIS investigators did not follow the BONBIS QA guidelines and delineated the CTV1 without taking into account the lead wires. As they defined CTV1 based only on the visible breast parenchyma, CTV1 was smaller than the reference CTV1. Consequently, variations were also noticed in dose volume histograms (DVH) with lower lung exposure (isodose 20 Gy lower than the expected value), although the V95% for CTV1 was adequate. Similar findings were reported in the multicenter and multi-observer RTOG study [10]. To facilitate breast CTV delineation, the recent ESTRO guidelines recommend to use the ventral side of the major pectoral muscle as the dorsal border of the breast volume in addition to radio-opaque markers around the mammary gland [11]. Although patients' enrolment was ended before these ESTRO guidelines, some investigators included the major pectoral muscle in the CTV1. However, no DVH variation was observed concerning CTV1.

Accurate delineation of the boost area is essential for the local control of invasive breast carcinoma, as indicated by previous studies on WBRT with simultaneous integrated boost [12], and accelerated partial breast irradiation [13–15]. Before the systematic use of surgical clips within the lumpectomy cavity, different surrogates were used to define the tumor boost location, such as the breast scar [16], ultrasound or CT scan imaging [17,18]. The placement of surgical clips in the lumpectomy cavity [19–21] improved the conformity index and decreased the inter-observer variability in the definition of the lumpectomy cavity after BCS [14]. The BONBIS QA program highlighted that most investigators did not take into account all surgical clips and delineated the tumor bed volume around surgical clips, and consequently CTV2 was larger than expected.

The randomized EORTC 22881-10882 trial (boost versus no boost) demonstrated that in invasive breast cancer, a localized boost decreases local recurrences, but the acute side effects related to the boost were not detailed [22,23]. To our knowledge, this is the first time that boost-related acute toxicities and their related predictive factors are analyzed in a very large phase 3 randomized study focused only on radiotherapy (without any associated endocrine or systemic adjuvant therapies). We found that smoking history, boost addition, and large breast CTV were strong predictive factors of grade ≥2 acute skin toxicities. A recent study tried to develop predictive models for acute skin toxicities using predictive factors reported in the literature, and to validate them in patients

Table 2
Acute toxicities.

		ARM A (WBRT) $n = 990$		ARM B (WBRT + BOOST) $n = 939$		p-value
		N	%	*N*	%	
Breast erythema						<0.001
	Grade 0	166	16.8	133	14.2	
	Grade 1	580	58.7	395	42.1	
	Grade 2	222	22.4	360	38.3	
	Grade 3	21	2.1	51	5.4	
	Missing	*1*		*0*		
Dermatitis						<0.001
	Grade 0	975	98.6	877	93.4	
	Grade 1	7	0.7	36	3.8	
	Grade 2	6	0.6	22	2.3	
	Grade 3	1	0.1	4	0.4	
	Missing	*1*		*0*		
Hyperpigmentation						0.005
	Grade 0	622	62.9	562	59.9	
	Grade 1	331	33.5	312	33.2	
	Grade 2	36	3.6	65	6.9	
	Missing	*1*		*0*		

WBRT: whole breast radiotherapy.

Table 3
Univariate analysis of acute toxicities.

	Acute skin toxicities Grade 0–1 (*N* = 1166)		Acute skin toxicities Grade ≥2 (*N* = 762)				
	N	%	*N*	%	OR	95%CI	*P value*
Age					0.99	[0.99–1.00]	0.27
BMI							<0.001
Underweight/Normal	703	64.9	329	45.7	1		
Overweight (≥25)	380	35.1	391	54.3	2.20	[1.81–2.67]	
Missing	*83*		*42*				
Breast size (bra and/or cup)							<0.001
Small	447	49.9	188	30.6	1		
Large	449	50.1	426	69.4	2.26	[1.82–2.80]	
Missing	*270*		*148*				
Hypertension							0.01
No	896	76.8	547	71.8	1		
Yes	270	23.2	215	28.2	1.30	[1.06–1.61]	
Missing	-		-				
Diabetes							<0.001
No	1124	96.5	708	92.9	1		
Yes	41	3.5	54	7.1	2.09	[1.38–3.17]	
Missing	1		0				
Smoking habits							0.17
Non-smoker	787	68.8	492	65.9	1		
Active smoker or History of smoking	356	31.2	255	34.1	1.15	[0.94–1.39]	
Missing	23		15				
Hormone replacement therapy							0.05
No	892	76.8	608	80.5	1		
Yes	269	23.2	147	19.5	0.80	[0.64–1.00]	
Missing	5		7				
Boost							<0.001
No	692	59.5	294	38.7	1		
Yes	472	40.5	466	61.3	2.32	[1.93–2.80]	
Missing	2		2				
Boost technique							<0.001
Photon	237	50.2	292	62.8	1		
Electron	190	40.3	129	27.7	0.55	[0.42–0.73]	
Mix	45	9.5	44	9.5	0.79	[0.51–1.24]	
Missing	6		1				
CTV1 (cm^3)							<0.001
<500	575	59.7	244	38.3	1		
≥500	388	40.3	393	61.7	2.39	[1.94–2.93]	
Missing	203		125				
CTV2 (cm^3)							<0.001
≤25	214	57.7	169	43.8	1		
>25	157	42.3	217	56.2	1.75	[1.31–2.33]	
Missing	101		80				

BMI: Body mass index.

Table 4
Multivariable analysis of acute toxicities.

	N = 1569		
	OR	95%CI	*P value*
Smoking habits			0.012
Non-smoker	1		
Active smoker or History of smoking	1.34	[1.07–1.68]	
Boost			<0.001
No	1		
Yes	2.51	[2.03–3.11]	
CTV1 (cm^3)			<0.001
<500	1		
≥500	2.60	[2.10–3.23]	

with breast cancer enrolled in the REQUITE study [24]. The final predictive model included age (<or >50 years), BMI, breast size, fractionation schedule, boost, smoking status, and tamoxifen use; however, it could not be validated as a risk model for acute skin toxicities during adjuvant radiotherapy.

Smoking has been associated with higher risk of second primary cancer related to ionizing radiation exposure (HR = 1.79, $p = 0.04$) [25], and breast radiotherapy significantly increases the risk of lung squamous cell carcinoma [26]. The relationship between the risk of grade ≥2 acute skin toxicities and smoking habits has been described only in a small prospective cohort (n = 377 patients, including 51 smokers) [27]. In this study, the risk of grade ≥2 epidermitis was significantly increased (OR = 2.71), as confirmed now by the BONBIS trial showing that smoking habits significantly increase this risk by 15%.

The correlation between large breast size and moist desquamation or grade 3 acute toxicities has been mainly described in small patients' cohorts to assess hypofractionated breast radiotherapy. These studies found that the risk of moist desquamation or grade 3 acute toxicity is higher in patients with breast volume >2500 mL, regardless of radiotherapy fractionation [28,29]. Fur-

thermore, boost administration, breast volume (larger than 800 cc), and surgical deficit significantly increased acute toxicity occurrence (multivariate analysis, n = 212 patients) [30]. The risk of grade $\geq$2 acute skin toxicities is higher after normofractionated than after hypofractionated WBRT [31]. The grade 2 and 3 acute skin toxicity rates observed in the BONBIS trial were similar to those described in this last study, particularly after the hypofractionated radiotherapy. Altogether, the previous results and our data indicate that in patients with breast cancer, the risk of grade $\geq$2 acute skin toxicities is significantly higher when breast volume is >500 cc.

In conclusion, the addition of a boost to the tumor bed significantly increased the severity of acute skin toxicities. Smoking history and large breast CTV were significant predictive factors of these events. Furthermore, the QA showed the need of a DR before patients' inclusion in a large multicentric phase III radiotherapy clinical trial to reduce the risk of major TP deviations.

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Conflict of interest

None.

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Appendix A. Supplementary data

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