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Original Article

Quality assurance of radiation therapy after breast-conserving surgery among patients in the BOOG 2013-08 trial

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ABSTRACT

Background and purpose: In the BOOG 2013-08 trial (NCT02271828), cT1-2N0 breast cancer patients were randomized between breast conserving surgery with or without sentinel lymph node biopsy (SLNB) followed by whole breast radiotherapy (WBRT). While awaiting primary endpoint results (axillary recurrence rate), this study aims to perform a quality assurance analysis on protocol adherence and (incidental) axillary radiation therapy (RT) dose.

Materials and methods: Patients were enrolled between 2015 and 2022. Data on prescribed RT and (in 25% of included patients) planning target volumes (PTV) parameters were recorded for axillary levels I-IV and compared between treatment arms. Multivariable linear regression analysis was performed to determine prognostic variables for incidental axillary RT dose.

Results: 1,439/1,461 included patients (98.5%) were treated according to protocol and 87 patients (5.9%) received regional RT (SLNB 10.9%, no-SLNB 1.5 %). In 326 patients included in the subgroup analysis, the mean incidental PTV dose at axilla level I was 59.5% of the prescribed breast RT dose. In 5 patients (1.5%) the mean

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PTV dose at level I was ≥95% of the prescribed breast dose. No statistically or clinically significant differences regarding incidental axillary RT dose were found between treatment arms. Tumour bed boost (yes/no) was associated with a higher incidental mean dose in level I ($R^2 = 0.035$, $F(6, 263) = 1.532$, p 0.168).
Conclusion: The results indicate that RT-protocol adherence was high, and that incidental axillary RT dose was low in the BOOG 2013-08 trial. Potential differences between treatmentarms regarding the primary endpoint can thus not be attributed to different axillary radiation doses.

Introduction

In patients with clinically node-negative (cN0) breast cancer a sentinel lymph node biopsy (SLNB) is traditionally performed to determine the pathological lymph node (pN) status, to guide adjuvant treatment recommendations.[1] Results from landmark trials such as ACOSOG Z0011 demonstrated that cN0 patients treated with breast-conserving surgery (BCS) and whole breast radiation therapy (WBRT) who have limited sentinel lymph node(s) (SLN(s)) metastases, do not benefit from a completion axillary lymph node dissection (cALND).[2,3] The added value of the SLNB itself was subsequently questioned in cN0 breast cancer patients and resulted in several randomized controlled trials investigating the safety of omitting the SLNB in cT1-2N0 patients in terms of axillary recurrence rate (INSEMA (NCT02466737), SOUND (NCT02167490), and BOOG 2013-08 (NCT02271828)).[4–6] In trials investigating omission of regional treatment, detailed radiation therapy (RT) data are pivotal to interpret long-term outcomes. This was emphasized by the ACOSOG Z0011 trial, in which 18.9% of a retrospectively analysed subset of patients was actually treated with non-protocol allowed nodal fields. Furthermore, 50% and 52.6% of the patients randomised to cALND and SLNB, were treated with 'high tangents' in which the cranial border was extended to ≤2 cm from the humeral head and which includes (part of) the low axilla. Both protocol deviations may potentially have biased results.[7] In 2020, the results from a RT quality assurance study of a subpopulation of the INSEMA trial were published, however, there are no RT data available from the SOUND trial.[4].

For patients randomized to the no-SLNB arm in the BOOG 2013-08 trial (and the INSEMA and SOUND trials), it is plausible that (residual) axillary lymph node metastases are left untreated. However, as part of WBRT, the ipsilateral axilla may to a certain extent receive incidental RT dose[7,8], which can potentially eradicate occult residual metastases and thus impact axillary recurrence rates. In the systematic review of Van Wely et al., a lower rate of axillary recurrences in SLN-negative patients treated with WBRT were reported compared to patients not treated with WBRT.[9] In a retrospective analysis of 4,129 patients treated with WBRT compared to intraoperative partial breast irradiation, the axillary recurrence rate was significantly lower following WBRT (1.3% versus 4.0%, $p < 0.001$).[10] Incidental RT doses to the axilla associated with WBRT may thus have contributed to these low axillary recurrence rates which was also found in trials such as ACOSOG Z0011.[2,3,11].

Some studies suggest that even in contemporary WBRT, the axilla receives a significant incidental RT dose.[4,8] Hence, patients included in the BOOG 2013-08 trial may have received an unintentional, but clinically relevant RT dose to the (lower part of) ipsilateral axilla as part of WBRT. Therefore, the aim of this quality assurance study was to investigate the RT protocol adherence and the extent of the incidental RT dose to the ipsilateral axilla within the BOOG 2013-08 trial.

Methods

Data for this study were derived from the BOOG 2013-08 trial, a non-inferiority, multicentre, randomized controlled trial (NCT02271828) [6], and was approved by the medical ethics committee of the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital (NL49315.031.14/M14CNB). After obtaining informed consent prior to inclusion, 1,733 cT1-2N0 patients were enrolled between May 2015 and January 2022. Patients were assigned to BCS, either with or without SLNB. Adjuvant completion axillary treatment (i.e., axillary RT level I-II with or without level III and IV, or cALND) and systemic treatment were recommended according to the national guidelines that were in effect during the study period.[1] A cALND was indicated in case of pN2(sn)). In case of macrometastases or >2 micrometastases (pN1(sn)) regional radiotherapy was indicated and based on the presence of risk factors, this could consist of regional radiotherapy or cALND.

The primary endpoint of the BOOG 2013-08 trial is the axillary recurrence rate at five years. The current study involves a quality assurance analysis on RT protocol adherence regarding the prescribed and administered locoregional RT doses, including incidental ipsilateral axillary RT dose. Patients with incomplete RT records or ineligible patients were not included in the current analysis.

Postoperative radiation therapy

WBRT was mandatory for all patients included in the BOOG 2013-08 trial. Patients treated with partial breast RT (BPI) were not eligible for inclusion. In the Netherlands, in general, treatment planning for WBRT consisted of inverse or forward IMRT with or without arcs, e.g. standard tangent fields complemented with partial arcs or complementary static beams. Daily imaging was standard practice for position verification, either with AP and lateral imaging or using CBCT. All centres applied some method for deep inspiration breath-hold to spare the heart.

A boost dose to the tumour bed was indicated dependent on the presence of risk factors (RF) (e.g., age <40 or 50 years,[12] Bloom-Richardson grade 3,[12] presence of lymphovascular invasion,[1] (focally) positive surgical resection margins,[1] or triple negative disease).[1] Regional RT was indicated dependent on the SLNB outcome: in case of micrometastasis with ≥1 RF (i.e., grade 3, age ≤40 years, triple negative disease, presence of lymphovascular invasion), or in case of ≤2 macrometastases without RF, RT of axilla level I and II was indicated, and in case of ≤2 macrometastases with RF, or in case of >2 metastases, RT of level I-IV was indicated.[13] Irradiation of internal mammary nodes was indicated in case of positive internal mammary lymph nodes. In case of a negative SLNB (including the presence of isolated tumour cells (pN0(i +)), or micrometastases without RF, no adjuvant regional RT was indicated, which is in accordance with the tumour classification guidelines.[14] In patients randomized to the no-SLNB-arm, no adjuvant regional RT was indicated. The protocol for adjuvant RT required a fractionation scheme biologically equivalent to 25 x 2 Gy given in 5 fractions per week. The boost dose (if indicated) was biologically equivalent to 8 x 2 Gy or 13 x 2 Gy.

All patients required a computed tomography (CT) scan after BCS for RT planning. In all patients (regardless of treatment arm and regardless of regional RT recommendations), the clinical target volumes (CTVs) of the breast, the tumour bed[15] (in case a boost was indicated), and all lymph nodes levels including axillary levels I-IV, and interpectoral nodes, were delineated separately according to the European Society for Radiotherapy and Oncology (ESTRO) atlas.[16] Planning target volumes (PTV) were defined by adding a margin of 5–7 mm to the CTVs. Additionally, delineation of the heart and lungs was obligatory.[5,17] The PTV dose (breast +/- nodes) was aimed to be between 95% and 107% of the prescribed RT dose.

Data acquisition

Patient and tumour characteristics as well as the *prescribed* and the *actually administered* RT dose to the breast and lymph nodes were collected. All RT data were prospectively abstracted from RT plans using predefined CRFs. For both treatment arms, deviations from the study protocol were recorded (e.g., prescription of regional RT when not indicated according to the protocol). The *actually administered* RT dose refers to the estimated dose distribution according to the approved treatment plan. The subgroup analyses of *actually administered* (incidental) RT dose concern the first 25% of included patients from each participating RT centre. Regarding the administered RT dose, several dose-volume histogram (DVH) parameters were collected for all delineated volumes. For the PTVs, the mean (incidental) dose, and the volume (as percentage of total volume) receiving at least 50%, 95% and 107% of the prescribed RT dose (V50%, V95%, V107%, respectively) were recorded. For all delineated lymph node volumes, the number of patients was reported for whom the V95% and V50% of the prescribed breast RT dose was ≥95%, ≥80% or ≥50%. Lymph node volumes with an incidental RT dose of V95%≥80%, which was arbitrarily chosen as cut-off, were considered as incidentally treated with a therapeutic dose. DVH parameters of the lymph node volumes in patients who were intentionally treated with regional RT were reported separately. To account for different fractionation schemes, the administered RT dose was reported as absolute value as well as percentage of the prescribed breast RT dose.

Statistical analysis

For this study, statistical analyses were performed according to the as-treated principle. To get an impression of the generalisability of the study population, tumour characteristics of this cohort were compared with tumour characteristics of all patients with cT1-2N0 breast cancer treated at Maastricht University Medical Centre^{+} (MUMC^{+}) between 2015 and 2021.

Finally, incidental RT DVH parameters were compared between the treatment arms using a Mann-Whitney *U* test. Predefined, and chosen based on literature or clinical relevance, clinicopathological factors potentially associated with higher incidental mean dose to axilla level I (as percentage of the prescribed breast dose), such as treatment arm, pN status, body mass index (BMI),[4,8,18] and boost on the tumour bed (yes/no),[4,8,18] were analysed using multivariable linear regression.

All analyses were performed using IBM Statistical Package for the Social Sciences Statistics version 28.0.

Results

Of the 1,733 patients who were included in the BOOG 2013-08 trial, 49 patients (2.8%) were excluded from analysis based on in- or exclusion criteria deviations (see Fig. 1 for the CONSORT diagram). Overall, an additional 12.9% (N = 223) of patients was excluded from the quality assurance analyses due to unknown or incomplete RT data.

Baseline patient- and tumour characteristics of the remaining 1,461

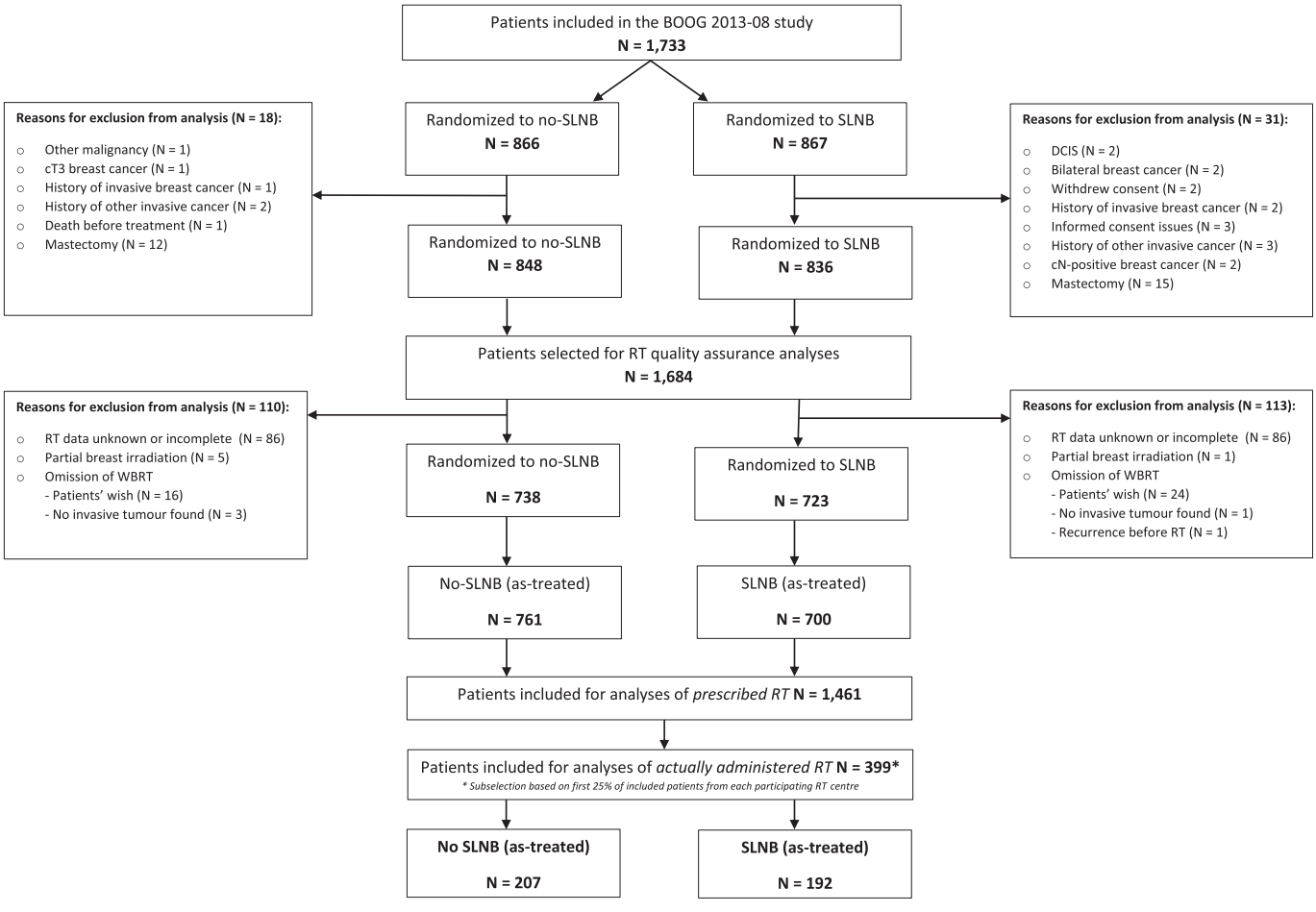

Fig. 1. Abbreviations: N number of patients; SLNB sentinel lymph node biopsy; DCIS ductal carcinoma in situ; RT radiation therapy; WBRT whole breast radiation therapy.

Table 1
Baseline clinicopathological characteristics of BOOG 2013-08 patients selected for radiation therapy quality assurance according to as-treated analysis Note: Missing values were not included for calculation of the percentages.

Parameter	Overall (N = 1,461)	SLNB (N = 700)	No-SLNB (N = 761)
Age in years			
Mean; SD (range)	61.4; 9.4 (30–87)	61.3; 9.6 (30–85)	61.5; 9.3 (32–87)
BMI			
Mean; SD	27.0; 5.0	26.9; 5.1	27.1; 4.9
Clinical tumour stage, N (%)			
o T1	1,193 (81.7 %)	572 (81.7 %)	621 (81.6 %)
o T2	268 (18.3 %)	128 (18.3 %)	140 (18.4 %)
Histological subtype, N (%)			
o Invasive ductal carcinoma/ NST	1,146 (78.9 %)	551 (79.3 %)	595 (78.6 %)
o Invasive lobular carcinoma	177 (12.2 %)	80 (11.5 %)	97 (12.8 %)
o Other	129 (8.9 %)	64 (9.2 %)	65 (8.6 %)
o Missing	9	5	4
Pathological grade (Bloom Richardson), N (%)			
o Grade 1	493 (37.0 %)	245 (38.8 %)	248 (35.3 %)
o Grade 2	657 (49.3 %)	299 (47.5 %)	358 (51.0 %)
o Grade 3	183 (13.7 %)	87 (13.8 %)	96 (13.7 %)
o Missing	128	69	59
Hormone receptor status, N (%)			
o HR + and HER2-	1,174 (86.9 %)	559 (86.7 %)	615 (87.1 %)
o HR- and HER2+	19 (1.4 %)	10 (1.6 %)	9 (1.3 %)
o HR + and HER2+	72 (5.3 %)	36 (5.6 %)	36 (5.1 %)
o Triple negative	86 (6.4 %)	40 (6.2 %)	46 (6.5 %)
o Missing	110	55	55
Neo-adjuvant therapy, N (%)			
o No neo-adjuvant therapy	1,286 (88.0 %)	608 (86.9 %)	678 (89.1 %)
o Chemotherapy	79 (5.4 %)	39 (5.6 %)	40 (5.3 %)
o Immuno- or targeted therapy	–		
o Hormonal therapy	44 (3.0 %)	25 (3.6 %)	19 (2.5 %)
o Chemo- and immuno- or targeted therapy	51 (3.5 %)	28 (4.0 %)	23 (3.0 %)
o Chemo- and hormonal therapy	1 (0.1 %)	–	1 (0.1 %)
Pathological N stage, N (%)			
o pN0	557 (38.3 %)	557 (79.7 %)	–
o pN0(+i)	29 (2.0 %)	29 (4.1 %)	–
o pN1mi	41 (2.8 %)	41 (5.8 %)	–
o pN1	51 (3.5 %)	49 (7.0 %)	2 (0.3 %)*
o pN2	–	–	–
o pNx	783 (53.4 %)	24 (3.4 %)	759 (99.7 %)
Additional axillary treatment, N (%)			
o No additional axillary treatment	1,365 (93.4 %)	616 (87.9 %)	750 (98.6 %)
o ALND only	9 (0.6 %)	9 (1.3 %)	–
o Regional RT only	80 (5.5 %)	69 (9.9 %)	11 (1.5 %)
o ALND and regional RT	7 (0.5 %)	7 (1.0 %)	–
Adjuvant therapy, N (%)			
o No adjuvant therapy	759 (52.0 %)	364 (52.0 %)	395 (51.9 %)
o Chemotherapy	46 (3.1 %)	20 (2.8 %)	26 (3.4 %)
o Immuno- or targeted therapy	10 (0.7 %)	7 (1.0 %)	3 (0.4 %)
o Hormonal therapy	474 (32.3 %)	221 (31.3 %)	253 (33.2 %)
o Chemo- and immuno- or targeted therapy	13 (0.9 %)	5 (0.7 %)	8 (1.0 %)
o Chemo- and hormonal therapy	97 (6.6 %)	50 (7.1 %)	47 (6.2 %)
o Immuno- and hormonal therapy	38 (2.6 %)	20 (2.8 %)	18 (2.4 %)
o Chemo, immuno- or targeted, and hormonal therapy	24 (1.6 %)	13 (1.8 %)	11 (1.4 %)

Note: Missing values were not included for calculation of the percentages.
AbbreviationsN number of patientsSLNB sentinel lymph node biopsySD standard deviationBMI body mass indexNST no special typeHR hormone receptorHER2 human epidermal growth factor receptor 2ALND axillary lymph node dissectionRT radiation therapy* Positive non-sentinel lymph node(s) found in breast specimen.

patients were summarized in Table 1 and supplementary table A. The proportion of patients with favourable tumour characteristics (e.g., grade 1, T1 tumour) was statistically significantly higher among the BOOG 2013-08 study population compared to similar breast cancer patients treated at the MUMC^{+} during the same time period (Supplementary table B). In addition, the percentage of patients with a positive pathological lymph node status was higher in the MUMC^{+} population than in the SLNB arm of the BOOG 2013-08 study (18.2% vs 12.8%).

In the SLNB arm, SLNB was performed in 691 patients (96.1%) and omitted in 28 patients (3.9%). In the no-SLNB arm, SLNB was performed in nine patients (1.2%) and omitted in 733 patients (98.8%). In total, SLNB was performed in 700 patients and omitted in 761 patients.

Results according to the as-treated principle showed that in the SLNB arm, 586 of 700 patients (including 29 patients with (pN0(i+)) (83.7%) had a pN0 status and 90 patients (17%) had pathological involvement (micrometastases 34.5% (N = 41), and one to three macrometastases 41.1% (N = 49) (including four patients with positive non-SLNs)). None of the patients had more than three lymph node macrometastases in the SLN. In 24 patients (3.4%), the SLN could not be evaluated. In the no-SLNB arm, the breast specimen of three patients (0.4%) contained non-SLN(s). In two of these patients, pathological macrometastases were found, resulting in a pN1 status in 0.3% of the patients in the no-SLNB arm.

In the SLNB arm, 16 patients (2.3%) underwent an cALND due to positive SLN(s) (N = 11), palpable lymph nodes during surgery (N = 1), patient's wish (N = 1), or unknown reasons (N = 3). The cALND contained additional metastases in eight of the 16 patients (1 positive LN N = 5, 2 positive LNs N = 2, 5 positive LNs N = 1). Five pN1 patients

(0.7%) refrained from cALND: one patient was treated with regional RT instead. In the no-SLNB arm, none of the patients underwent an cALND. Supplementary table C holds the baseline patient- and tumour characteristics of pN-negative and pN-positive BOOG 2013-08 patients according to as-treated analysis.

The majority (91.1%) of all patients, irrespective of SLNB-procedure, received moderate hypofractionated RT (consisting of 15 or 16 fractions) (see Table 2). In 39.6% of all patients, a boost to the tumour bed was prescribed.

A total of 87 of 1,461 patients (6.0%) were intentionally treated with regional RT: 76/700 patients (10.9%) in the SLNB arm and 11/761 patients (1.5%) in the no-SLNB arm (Table 2). Sixty-nine of these 87 patients (79.3%) had a positive pN status (including both patients in the no-SLNB arm with positive non-SLN(s) found in the breast specimen). The remaining 18 of these 87 patients did not have a formal indication for regional RT: nine in the SLNB arm (negative pN status N = 7, pNX status N = 2) and nine in the no-SLNB arm (all with a pNX status). Reasons for regional RT in these patients were unknown. Another four of 1,461 patients (N = 4 in the SLNB arm) were not treated with regional RT while these patients had a formal indication for regional RT (micrometastases with RF (N = 1) or macrometastases (N = 3)). These patients also did not undergo an cALND. Reasons for omitting regional treatment in these patients were unknown. In conclusion, 22 of 1,461 patients (1.5%) were not treated according to protocol (SLNB 1.9%, no-SLNB 1.2%).

A total of 399 out of the 1,461 patients from all ten participating radiation therapy centres were selected for analysis regarding the PTV RT dose distribution, based on the first 25% of inclusion per RT centre. One centre was excluded from analysis (N = 51), since PTV data were missing. Finally, 348 patients from 9 RT centres were included in the following analysis (N = 168 in the SLNB arm, and N = 180 in the no-SLNB arm). A total of 22 of the 348 patients (SLNB arm N = 20, no-SLNB arm N = 2) were intentionally treated with regional RT and are not reported in this study. A total of six patients had a positive pathological lymph nodes status but were not intentionally treated with regional RT (N = 1 micrometastasis without RF, N = 5 patients with macrometastases).

The mean breast PTV dose was 102.5% (range 96.9 – 125.5) of the prescribed breast dose and did not differ significantly between the treatment arms (Table 3). Ten of 326 patients (3.1%) had a V95% between 89 and 94%, the remaining patients had a V95%≥95%. As demonstrated in Table 3, there were no statistically significant differences between the treatment arms for the breast PTV coverage, except for a small difference in V95%, which was statistically significantly higher in the SLNB arm compared to the no-SLNB arm (98.4% compared to 97.8% $p = 0.002$).

The mean incidental PTV dose at axillary level I was approximately 60% of the prescribed breast RT dose in both arms, and this dose decreased to approximately 2% at level IV. The mean incidental PTV dose was ≥95% of the prescribed breast dose in five of 326 patients (1.5%) at axilla level I, compared to one patient (0.3%) at level II, eight patients (2.5%) at the interpectoral lymph nodes, one patient (0.3%) at level II, and 0 patients at level IV. No statistically significant differences between the SLNB arm and the no-SLNB arm were found regarding incidental dose to the ipsilateral lymph node volumes, apart from level II, in which the V95% was significant higher in the SLNB arm (see Table 3). None of the patients in the SLNB and no-SLNB-arms received an incidental V95% ≥ 95% at any of the axilla volumes. A small number of patients (N = 5, 1.5%) were incidentally treated with a therapeutic dose at level I and/or the interpectoral lymph nodes (V95% ≥ 80). Supplementary tables D and E provide an overview of the prescribed and actually administered RT data for SLNB-patients divided by SLNB-negative and SLNB-positive (not regionally treated) patients. Intention to treat analyses of the actually administered RT demonstrated similar results as the analyses performed according to as treated principle (supplementary table E).

The multivariable linear regression analyses demonstrated that a boost on the tumour bed was statistically significantly associated with a higher incidental dose in axilla level I (p 0.036) (see supplementary table F). BMI, the presence of (pN0(i+)), micrometastases or macrometastases in the SLN were not significantly associated with a higher incidental radiation dose in axilla level I.

Discussion

This quality assurance study demonstrated that in 98.5% (1,439/1,461) of all BOOG 2013-08 patients RT was prescribed according to study protocol. Three hundred and sixteen of the 326 patients (96.9%)

Table 2
Prescribed radiation therapy schemes and target volumes.

	Total (N = 1,461)	SLNB (N = 700)	No-SLNB (N = 761)
WBRT irradiation, N (%)			
o **Conventional fractionation***	-	-	-
o **Moderate hypofractionation**	1,275 (91.1 %)	600 (90.8 %)	675 (91.3 %)
o **One-week hypofractionation****	125 (8.9 %)	61 (9.2 %)	64 (8.7 %)
o **Other*****	61	39	22
Boost, N (%)			
o **Yes**	544 (39.6 %)	258 (39.6 %)	286 (39.6 %)
o **No**	829 (60.4 %)	393 (60.4 %)	436 (60.4 %)
o **Missing**	88	49	39
Regional radiotherapy, N (%)	87	76	11
o **Level I-II**	41 (2.8 %)	35 (5.0 %)	6 (0.8 %)******
o **Level I-II + Interpectoral nodes**	8 (0.6 %)	8 (1.1 %)	-
o **Level III-IV**	6 (0.4 %)	6 (0.9 %)	-
o **Level I-IV**	9 (0.6 %)	9 (1.3 %)	-
o **Level I-IV + Interpectoral nodes**	13 (0.9 %)	12 (1.7 %)	1 (0.1 %)
o **Level I-IV + Interpectoral nodes + Parasternal nodes**	9 (0.6 %)	5 (0.7 %)	4 (0.5 %)
o **Level I-IV + Parasternal nodes**	1 (0.1 %)	1 (0.1 %)	-
o **Missing**	-	-	-

Note: Missing values were not included for calculation of the percentages.
Abbreviations: SLNB sentinel lymph node biopsy, Nu number of patients; WBRT whole breast radiation therapy;
* None of the patients were treated according to the "traditional" 25 fraction scheme.
** One-week hypofractionation was only given in case no regional RT or a boost was indicated.
*** Target volumes known, fractionation scheme not yet available at time of analysis.
**** Positive non-sentinel lymph node(s) found in breast specimen, N = 1.

Table 3
Dose volume parameters of the planning target volumes in a subselection of BOOG 2013-08 participants.

Parameter	Overall N = 326	SLNB arm (pN- and pN+) N = 148	No-SLNB arm N = 178	*P-value*
Breast				
Mean dose in Gy, mean; SD (range)	44.1; 3.7 (28.5 – 56.5)	44.4; 3.4 (39.3 – 56.5)	43.8; 4.0 (28.5 – 55.8)	0.195
o percentage of prescribed breast dose, mean; SD (range)	102.5; 4.1 (96.9 – 125.5)*	102.7; 4.2 (98.1 – 124.1)*	102.3; 3.9 (96.9 – 125.5)*	0.189
V95 %, mean (%); SD (range)	98.1; 1.7 (89 – 100)	98.4; 1.3 (91 – 100)	97.8; 1.9 (89 – 100)	**0.002**
Axillary level I				
Mean dose in Gy, mean; SD (range)	25.6; 8.8 (2.5 – 46.1)	26.3; 8.8 (5.1 – 46.1)	25.0; 8.9 (2.5 – 45.6)	0.294
o percentage of prescribed dose, mean; SD (range)	59.5; 19.9 (5.9 – 101.2)	60.8; 19.6 (12.0 – 101.2)	58.4; 20.1 (5.9 – 100.1)	0.449
V95 %, mean (%); SD (range)	31.1; 18.1 (0 – 87)	33.4; 19.1 (0 -84)	29.3; 17.1 (0 – 87)	0.198
o V95 % >= 95 %	N = 0	N = 0	N = 0	
o V95 % >= 80 %	N = 3 (0.9 %)	N = 2 (1.4 %)	N = 1 (0.6 %)	
o V95 % >= 50 %	N = 46 (14.1 %)	N = 28 (18.9 %)	N = 18 (10.1 %)	
V50 %, mean (%); SD (range)	58.2; 21.3 (7-100)	59.2; 21.1 (8-97)	57.4; 21.5 (7-100)	0.663
o V50 % >= 95 %	N = 11 (3.4 %)	N = 6 (4.1 %)	N = 5 (2.8 %)	
o V50 % >= 80 %	N = 51 (15.6 %)	N = 23 (15.5 %)	N = 28 (15.7 %)	
o V50 % >= 50 %	N = 159 (48.8 %)	N = 74 (50.0 %)	N = 85 (47.8 %)	
Axillary level II				
Mean dose in Gy, mean; SD (range)	14.8; 8.2 (1.3 – 51.0)	15.9; 8.1 (1.3 – 51.0)	13.9; 8.2 (1.4 – 36.0)	0.075
o percentage of prescribed dose, mean; SD (range)	34.4; 19.1 (3 – 119.7)	36.8; 18.6 (3.1 – 119.7)	32.5; 19.3 (3.0 – 83.4)	0.091
V95 %, mean (%); SD (range)	7.6; 10.0 (0 – 69)	8.9; 10.2 (0 – 46)	6.6; 9.7 (0 - 69)	**0.034**
o V95 % >= 95 %	N = 0	N = 0	N = 0	
o V95 % >= 80 %	N = 0	N = 0	N = 0	
o V95 % >= 50 %	N = 1 (0.3 %)	N = 0	N = 1 (0.6 %)	
V50 %, mean (%); SD (range)	31.9; 20.6 (0-95)	33.5; 19.3 (0-95)	30.7; 21.7 (0-91)	0.236
o V50 % >= 95 %	N = 1 (0.3 %)	N = 1 (0.7 %)	N = 0	
o V50 % >= 80 %	N = 3 (0.9 %)	N = 1 (0.7 %)	N = 2 (1.1 %)	
o V50 % >= 50 %	N = 51 (15.6 %)	N = 25 (16.9 %)	N = 26 (14.6 %)	
Interpectoral lymph nodes				
Mean dose in Gy, mean; SD (range)	25.0; 10.6 (1.0 – 48.0)	25.6; 10.3 (1.0 – 47.2)	24.4; 10.9 (1.5 – 48.0)	0.266
o percentage of prescribed dose, mean; SD (range)	58.1; 24.5 (2.3 – 105.3)	59.3; 23.4 (2.3 – 101.1)	57.1; 25.5 (3.3 – 105.3)	0.319
V95 %, mean (%); SD (range)	28.6; 21.6 (0 – 94)	30.7; 21.0 (0 – 94)	27.0; 22.0 (0 – 82)	0.288
o V95 % >= 95 %	N = 0	N = 0	N = 0	
o V95 % >= 80 %	N = 2 (0.6 %)	N = 1 (0.7 %)	N = 1 (0.6 %)	
o V95 % >= 50 %	N = 44 (13.5 %)	N = 22 (14.9 %)	N = 22 (12.4 %)	
V50 %, mean (%); SD (range)	57.8; 26.7 (0-100)	58.8; 25.9 (0-100)	57.0; 27.5 (0-100)	0.390
o V50 % >= 95 %	N = 14 (4.3 %)	N = 5 (3.4 %)	N = 9 (5.1 %)	
o V50 % >= 80 %	N = 65 (19.9 %)	N = 28 (18.9 %)	N = 37 (20.8 %)	
o V50 % >= 50 %	N = 158 (48.5 %)	N = 77 (52.0 %)	N = 81 (45.5 %)	
Axillary level III				
Mean dose in Gy, mean; SD (range)	3.5; 4.4 (0.1 – 45.9)	3.5; 3.7 (0.4 – 21.2)	3.5; 5.0 (0.1 – 45.9)	0.330
o percentage of prescribed dose, mean; SD (range)	8.2; 10.0 (0.2 – 98.3)	8.1; 8.4 (0.9 – 49.9)	8.2; 11.2 (0.2 – 98.3)	0.367
V95 %, mean (%); SD (range)	0.3; 1.4 (0 – 14)	0.2; 1.4 (0 – 14)	0.4; 1.5 (0 – 12)	0.184
o V95 % >= 95 %	N = 0	N = 0	N = 0	
o V95 % >= 80 %	N = 0	N = 0	N = 0	
o V95 % >= 50 %	N = 0	N = 0	N = 0	
V50 %, mean (%); SD (range)	3.9; 8.7 (0-62)	4.5; 9.9 (0-62)	3.5; 7.7 (0-44)	0.339
o V50 % >= 95 %	N = 0	N = 0	N = 0	
o V50 % >= 80 %	N = 0	N = 0	N = 0	
o V50 % >= 50 %	N = 2 (0.6 %)	N = 2 (1.4 %)	N = 0	
Axillary level IV				
Mean dose in Gy, mean; SD (range)	1.0; 0.5 (0.1 – 3.3)	1.0; 0.5 (0.3 – 3.3)	1.0; 0.5 (0.1 – 2.9)	0.959
o percentage of prescribed dose, mean; SD (range)	2.3; 1.1 (0.2 – 7.8)	2.3; 1.0 (0.7 – 7.8)	2.3; 1.2 (0.2 – 6.5)	0.851
V95 %, mean (%); SD (range)	0	0	0	1.000
o V95 % >= 95 %	N = 0	N = 0	N = 0	
o V95 % >= 80 %	N = 0	N = 0	N = 0	
o V95 % >= 50 %	N = 0	N = 0	N = 0	
V50 %, mean (%); SD (range)	0.05; 0.5 (0-6)	0	0.09; 0.7 (0-6)	0.151
o V50 % >= 95 %	N = 0	N = 0	N = 0	
o V50 % >= 80 %	N = 0	N = 0	N = 0	
o V50 % >= 50 %	N = 0	N = 0	N = 0	

Note: RT doses are expressed in Gy.
Abbreviations: SLNB sentinel lymph node biopsy; N number of patients; SD standard deviation; V95 % volume receiving at least 95 % of the prescribed RT dose; V50 % volume receiving at least 50 % of the prescribed RT dose.
* Percentages of prescribed dose ≥ 105 % due to boost.

included in a subgroup analysis with detailed RT data received a V95%≥ 95% in the breast. In the majority (98.5%) of all no-SLNB patients was, in line with study protocol, no additional axillary RT prescribed. Moreover, the incidental RT dose to the ipsilateral axilla was comparable between both treatment arms and none of the lymph node volumes was unintentionally treated with a V95%≥95%.

The INSEMA-, SOUND-, and BOOG 2013-08 trials all examine the oncologic safety of omitting SLNB in cT1-2N0 patients treated with BCS and WBRT.[4–6] Recently presented results from the SOUND trial showed no statistically significant difference in distant disease-free survival between the treatment arms.[19] The oncological safety outcomes from the INSEMA- and BOOG 2013-08 trial are not yet available

(the BOOG 2013-08 data are expected in 2025). In order to accurately interpret oncological outcomes, detailed RT data are necessary for all those trials. The INSEMA study group reviewed the target volumes of the prescribed and the actually administered RT of level I – III of the ipsilateral axilla of the first three RT planning records from each participating RT centre (i.e. about 5% of the total study population).[4] About 15% of the planning records revealed that patients were not treated according to the INSEMA protocol. At least 25% of the patients in the INSEMA trial were unintentionally treated with a median PTV dose of ≥95% of the prescribed breast radiation dose in axillary level I, and 25% of the patients with a median RT dose of ≥75% of the prescribed dose in axillary level II. Similar as in the BOOG 2013-08 trial, there were no statistically significant differences between the treatment arms regarding unintentional axillary RT.[4] In the BOOG 2013-08 trial, 1.5% of the patients were unintentionally treated with a mean PTV dose of ≥95% of the prescribed breast radiation dose at axillary level I. None of the patients received ≥95% of the prescribed breast radiation dose to ≥95% of level I (or any of the other nodal levels) unintentionally.

It is uncertain which doses should be considered as a therapeutic dose. In this study we assumed that when at least 80% of the PTV of interest received at least 95% of the prescribed RT dose, this could be considered as an adequate/therapeutic dose/volume coverage. With this definition, only five patients (1.5%) (SLNB N = 3, no-SLNB N = 2) could be considered as incidentally treated to a therapeutically sufficient level. However, it is possible that, at least in these low-risk breast cancer patients, lower dose/volume coverages may already have at least part of the therapeutic effect, also depending on the dose distribution within the PTV.

Comparison of RT data regarding axillary level IV, interpectoral- and parasternal lymph nodes was not possible as these levels were not reported in the INSEMA trial. In the no-SLNB arm, the mean incidental RT dose (as percentage of prescribed breast dose) in the INSEMA and BOOG 2013-08 trials was 64.6% and 58.4% for level I, 34.9% and 32.5% for level II, and 13.8% and 8.3% for level III, respectively. Thus, the incidental ipsilateral axillary RT dose in the BOOG 2013-08 trial was lower compared to doses reported in the INSEMA trial and other previously reported trials. This may be caused by the distinct difference in the amount of patients treated with a boost on the tumour bed between the INSEMA trial and the BOOG 2013-08 trial (39.6% compared to 88.1% in the INSEMA trial). In our multivariable analysis, tumour bed boost was significantly associated with higher incidental RT dose. Hildebrandt et al., (2020) mentioned that the rate of tumour bed boost was 'remarkable high' for the INSEMA cohort of patients.[4] Other factors that may explain the difference in incidental RT dose might be related to RT techniques, including adherence to target volume contouring. In the INSEMA trial, the majority of patients were treated with 3D-CRT treatment plans. The SOUND trial does not provide detailed information regarding treatment planning. In the BOOG 2013-08 trial, patients are generally treated with some form of IMRT.

Omission of the SLNB, and consequently the lack of information regarding the pN status, could affect the decision-making process regarding adjuvant (systemic) therapy. A study from van Roozendaal et al., suggested that only a small percentage (1–3.6%) of patients would be affected by omitting SLNB in the decision-making for adjuvant (systemic) treatment.[20] In the present study, as well as in the INSEMA trial, there were no statistically significant differences detected regarding systemic therapy prescription between the treatment-arms. Further analysis is needed to determine whether the multidisciplinary breast teams were more prone to use gene expression profiling in the non-SLNB arm to make up for the lack of information on the pN status. Regarding adjuvant surgical treatment, the present trial demonstrated that cALND was omitted in all patients randomized to the no-SLNB arm, while still 2.3% of patients in the SLNB arm underwent cALND even though results from the AMAROS trial showed that cALND can be safely replaced by axillary RT in a specific group of breast cancer patients without compromising the regional control. Regarding regional RT, this was prescribed in 1.5% of patients in the no-SLNB arm, which was substantially less than the SLNB-arm (11% of patients). Consequently, the benefits of omitting SLNB may extend beyond simply omitting a surgical axillary staging procedure and may result in omission of regional treatment in a broader perspective, which further contributes to optimizing breast cancer care.

This study has various strengths, such as the large number of included patients with detailed RT data available for each of the distinct nodal volumes, not only in terms of mean RT doses but also in terms of RT dose/volume parameters.

This study also has some limitations. The proportion of patients included in the BOOG 2013-08 trial that showed favourable tumour characteristics was higher compared to a similar sample of breast cancer patients who were (partially) not included but treated during the same time period. This may indicate selection bias, which has also been reported in other trials on axillary management.[21] Quality of contouring was not evaluated in this trial. Automatic contouring models may be valuable for clinical practice to further improve consistency in delineation. Future research is needed to determine whether this may lead to clinically relevant improvements. Another limitation is the increased use of one-week fractionation schemes in daily practice following the publication of the FAST-FORWARD trial. [22] All of the included patients prescribed with one-week hypofractionation RT (8.9%), were treated after April 2020, which corresponds with the (start of) COVID-19 pandemic. One-week fractionation may result in a different biologically equivalent incidental dose to the ipsilateral axilla. Further analyses are needed to compare different fractionation schemes regarding this aspect.

Conclusion

In the BOOG 2013-08 study RT protocol adherence was extremely high and the proportion of protocol violations with regard to prescribing regional RT in patients from the no-SLNB arm is with 1.2% clinically negligible. Moreover, the incidental axillary RT dose was generally very low as only 1.5% of the patients had a mean PTV dose of ≥95% of the prescribed breast dose at axilla level I. We did not find any statistically significant or clinically relevant differences in incidental RT dose between treatment arms, indicating that potential differences between treatment-arms regarding the primary endpoint cannot be attributed to different axillary radiation doses. Collecting and analysing detailed RT data remains a tremendously important aspect of ongoing and future studies on omission of SLNB.

Declaration of interest

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CRediT authorship contribution statement

V.M. Wintraecken: Methodology, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **L.J. Boersma:** Conceptualization, Funding acquisition, Writing – review & editing. **L.M. van Roozendaal:** Conceptualization, Funding acquisition, Writing – review & editing. **J. de Vries:** Conceptualization, Funding acquisition, Writing – review & editing. **S.M.J. van Kuijk:**

Conceptualization, Funding acquisition, Writing – review & editing. **M. L.G. Vane:** Conceptualization, Funding acquisition, Writing – review & editing. **T. van Dalen:** Conceptualization, Funding acquisition, Writing – review & editing. **J.A. van der Hage:** Conceptualization, Funding acquisition, Writing – review & editing. **L.J.A. Strobbe:** Conceptualization, Funding acquisition, Writing – review & editing. **S.C. Linn:** Conceptualization, Funding acquisition, Writing – review & editing. **M. B.I. Lobbes:** Conceptualization, Funding acquisition, Writing – review & editing. **P.M.P Poortmans:** Conceptualization, Funding acquisition, Writing – review & editing. **V.C.G. Tjan-Heijnen:** Conceptualization, Funding acquisition, Writing – review & editing. **K.K.B.T. van de Vijver:** Conceptualization, Funding acquisition, Writing – review & editing. **A.H. Westenberg:** Conceptualization, Funding acquisition, Writing – review & editing. **J.H.W. de Wilt:** Conceptualization, Funding acquisition, Writing – review & editing. **M.L. Smidt:** Conceptualization, Funding acquisition, Formal analysis, Supervision, Writing – review & editing. **J.M. Simons:** Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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