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Clinical Investigation

Central Review of Radiation Therapy Planning Among Patients with Breast-Conserving Surgery: Results from a Quality Assurance Process Integrated into the INSEMA Trial

Guido Hildebrandt, PhD,[*] Angrit Stachs, PhD,[†] Bernd Gerber, PhD,[†] Jochem Potenberg, MD,[‡] David Krug, PhD,[§] Kathi Wolter, MD,[*] Thorsten Kühn, PhD,[‖] Dietmar Zierhut, PhD,[¶] Felix Sedlmayer, PhD,[#] Julia Kaiser, MD,[#] Roland Reitsamer, PhD,[**] Jörg Heil, PhD,[††] Valentina Nekljudova, DSc,[‡‡] Inga Bekes, MD,[§§] Sibylle Loibl, PhD,[‡‡] and Toralf Reimer, MD, PhD[†]

**Department of Radiotherapy, University of Rostock, Rostock, Germany; [†]Department of Obstetrics and Gynecology, University of Rostock, Rostock, Germany; [‡]Breast Center, Evangelisches Waldkrankenhaus Spandau, Berlin, Germany; [§]Department of Radiation Oncology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; [‖]Department of Obstetrics and Gynecology, Interdisciplinary Breast Center, Esslingen, Germany; [¶]Department of Radio-Oncology and Radiotherapy, Klinikum Hanau GmbH, Hanau, Germany; [#]Department of Radiotherapy and Radio-Oncology, LKH Salzburg, Paracelsus Medical University Clinics, Salzburg, Austria; **Breast Center, LKH Salzburg, Paracelsus Medical University Clinics, Salzburg, Austria; [††]Breast Unit, University Hospital, University of Heidelberg, Heidelberg, Germany; [‡‡]German Breast Group, Neu-Isenburg, Germany; and [§§]Department of Obstetrics and Gynecology, University of Ulm, Ulm, Germany*

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Purpose: After publication of the radiation field design in the American College of Surgeons Oncology Group Z0011 trial, a radiation therapy quality assurance review was integrated into the Intergroup-Sentinel-Mamma (INSEMA) trial. We aimed to investigate the role of patient characteristics, extent of axillary surgery, and radiation techniques for dose distribution in ipsilateral axillary levels.

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Corresponding author: Toralf Reimer, MD, PhD; E-mail: toralf.reimer@med.uni-rostock.de

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Methods and Materials: INSEMA (NCT02466737) has randomized 5542 patients who underwent breast-conserving surgery. Of these, 276 patients from 108 radiation therapy facilities were included in the central review, using the planning records of the first 3 patients treated at each site.
Results: Of the 276 patients, 41 had major deviations (ie, no axillary contouring or submission of insufficient records) leading to exclusion. A total of 235 (85.1%) radiation therapy planning records were delineated according to the INSEMA protocol, including 9 (3.8%) cases with minor deviations. At least 25% of INSEMA patients were unintentionally treated with $\geq$95% of the prescribed breast radiation dose in axillary level I. Approximately 50% of patients were irradiated with a median radiation dose of more than 85% of prescription dose in level I. Irradiated volumes and applied doses were significantly lower in levels II and III compared with level I. However, 25% of patients still received a median radiation dose of $\geq$75% of prescription dose to level II. Subgroup analysis revealed a significant association between incidental radiation dose in the axilla and obesity. Younger age, boost application, and fractionation schedule showed no impact on axillary dose distribution.
Conclusions: Assuming $\geq$80% of prescribed breast dose as the optimal dose for curative radiation of low-volume disease in axillary lymph nodes, at least 50% of reviewed INSEMA patients received an adequate dose in level I, even with contemporary 3-dimensional techniques. Dose coverage was much less in axillary levels II and III, and far below therapeutically relevant doses.

Introduction

The Intergroup-Sentinel-Mamma (INSEMA) trial (NCT02466737, GBG75, ABCSG43) is a prospective, randomized trial comparing sentinel lymph node biopsy (SLNB) versus no axillary surgery in patients with early invasive breast cancer (clinically/imaging $\leq$5 cm, c/iN0) who are candidates for breast-conserving surgery (BCS) including postoperative whole-breast irradiation (WBI).[1] In a second phase, patients with involved sentinel lymph nodes (1-3 macrometastases) are randomized to either SLNB alone or completion axillary lymph node dissection (ALND). The rationale of the study is based on available data at the time of protocol design (2011-2014).[2,3]

After publication of the radiation field design in the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial,[4] with frequent use of protocol-prohibited nodal fields, a radiation therapy quality assurance review was integrated into the INSEMA protocol. Here, the first 3 radiation therapy planning records from each radiation oncology facility were submitted for central review of radiation field design and axillary contouring. Immediate response was provided to the local radio-oncologist in the event of protocol violations, such as extended coverage of the regional nodes or insufficient contouring of axillary levels.

Although the INSEMA protocol required that patients receive WBI using standard tangential fields, partial involvement of ipsilateral axillary levels within the finalized irradiated volume cannot be avoided in the majority of patients owing to individual anatomic conditions and was not considered as a protocol violation. Previous studies have shown that up to 73% of axillary level I and 26% of level II receive an elective radiation dose with conventional 2-dimensional (2D) WBI.[5-7] Meanwhile, 3-dimensional (3D) radiation therapy techniques have mostly replaced 2D radiation therapy. To clarify the impact of contemporary 3D radiation techniques on incidental radiation to the axilla, consistent contouring of the ipsilateral axilla (level I-III) was essential for all INSEMA patients, using Radiation Therapy Oncology Group (RTOG) consensus definitions for radiation therapy planning.[8]

We aimed to investigate the role of patient characteristics, extent of axillary surgery, and radiation techniques for dose distribution in ipsilateral axillary levels among the INSEMA subgroup selected for the central review process.

Methods and Materials

After approval by local independent review boards and after obtaining informed consent from patients, INSEMA enrolled patients between September 2015 and April 2019, with a total of 5542 randomly assigned (Fig. 1). Of these, 279 patients from 108 radiation therapy facilities were included in the quality assurance review of radiation therapy planning, equating to an average of 2.6 submitted records per radiation therapy institution. INSEMA patients were recruited in 142 German and 9 Austrian study sites.

Postoperative radiation therapy

Adjuvant radiation therapy in the INSEMA trial was mandatory for all patients, in line with the current German Working Group of Gynecologic Oncology (AGO) guidelines,[9] German S3 guideline,[10,11] and German Society of Radio-Oncology (DEGRO) practical guidelines.[12] All study patients were scheduled to receive computed tomography (CT)-based WBI with 3D conformal radiation therapy (3D-CRT) or intensity modulated radiation therapy (IMRT) to the remaining breast (50 Gy in 25 fractions or 50.4 Gy in 28 fractions). A hypofractionated regimen with a single dose of 2.66 Gy in 15 fractions as defined in the START B trial[13] could be used as an additional option. A boost to the tumor bed (recommended dose, 10-16 Gy) was indicated for all patients. Application of the simultaneously integrated boost (SIB) technique was allowed during

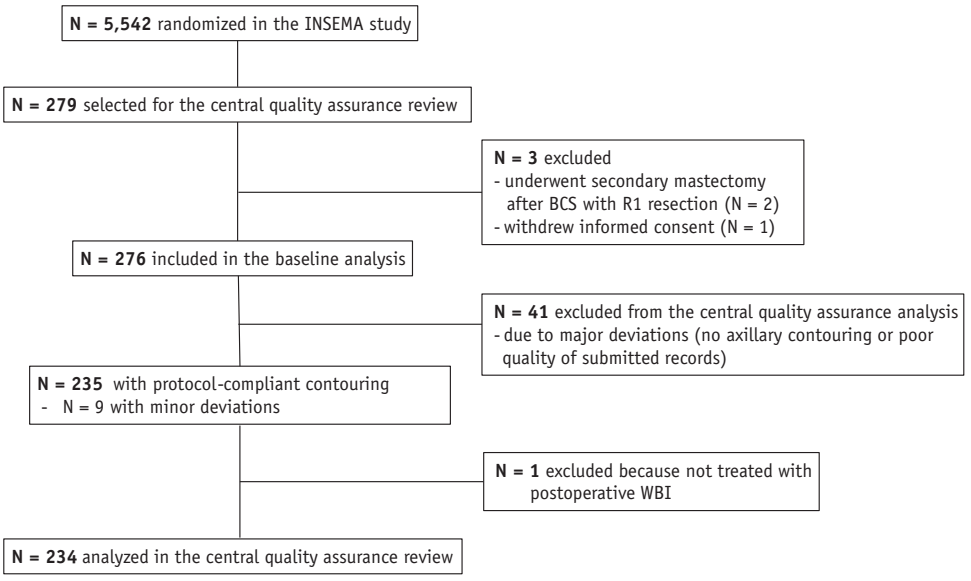

Fig. 1. CONSORT diagram. *Abbreviations:* BCS = breast-conserving surgery; WBI = whole-breast irradiation.

normofractionated WBI but not in the case of hypofractionation.[14] SIB doses of 10 to 16 Gy were administered in 25 to 28 fractions, leading to areas of daily zonal dose augmentation of 20% to 35% of the prescribed whole-breast dose. In selected cases at low risk for local recurrence (age >60 years, small tumor size, and favorable tumor biology), the boost application could be omitted. The use of partial breast irradiation alone was not allowed.

The INSEMA protocol required a treatment planning CT scan in the supine position to define the clinical target volumes (CTVs) and planning target volumes (PTVs). The breast CTV and contouring of the ipsilateral axilla (level I-III) should generally follow RTOG consensus guidelines.[8] The structures to be delineated (including breast, boost, and axillary levels I-III) are the same in all treatment arms. Dose-volume histogram parameters for every contour were entered into the electronic case report form: maximum, minimum, median, average dose (Gy), and volumes (mL). Pseudonymized radiation therapy reports were collected and analyzed centrally to evaluate the data for WBI (fractionation, technique) and for tumor bed boost (technique and dose, simultaneous or sequential application).

Hot spots in the axilla were assessed using the International Commission on Radiation Units and Measurements Report 50 (and 62) definition of a hot spot as a volume that received an excessive dose of radiation.[15] Accordingly, the maximal doses for each level were reviewed, and hot spots detected as >120% of prescribed breast dose were considered excessive.

The use of high tangents (defined as inclusion of level I and middle- to upper-level II axillary lymph nodes in the CTV) or comprehensive nodal irradiation (high tangents plus supraclavicular field) was not allowed,[16] with the exception of patients with 4 or more axillary lymph node metastases (≥pN2a). Regarding patients with 1 to 3 nodal metastases or with microscopic extranodal tumor extension beyond the lymph nodes, particularly when such findings are associated with a small primary tumor (≤5 cm), no general recommendation for postoperative nodal irradiation is given in the German S3 guideline or by international experts.[17] Axillary radiation therapy according to the AMAROS trial (axillary levels I-III with medial part of the supraclavicular fossa as CTV) was not allowed according to the INSEMA protocol.[18]

Radiation therapy quality assurance reviews

The first 3 3D-CRT/IMRT cases treated at each radiation oncology facility underwent central review. In this process, the finalized treatment plan was electronically submitted within 1 week of treatment initiation. These cases were reviewed in a timely manner at the Department of Radiation Therapy, University of Rostock, by 2 independent radiooncologists, and feedback was sent to the submitting radiation oncology facility. Each of the reviewed cases for quantification of axillary dose distributions underwent a rigorous check and double check to ensure it was within the defined guidelines for axillary nodal region contouring (Fig. 2). Corrections and resubmissions of data were requested for cases that did not meet contouring and protocol criteria.

Statistics

The analyses were performed using data available as of August 1, 2019. Continuous data between groups were compared with a Wilcoxon rank-sum test with t approximation. Fisher's exact test or a χ^2 test was used to compare categorical variables. Analyses were performed by German Breast Group (GBG) statisticians using SAS (Statistical Analysis Software, Cary, NC) version 9.4 with SAS Enterprise Guide 7.13. All tests were 2-sided, and P values less than .05 were considered statistically significant.

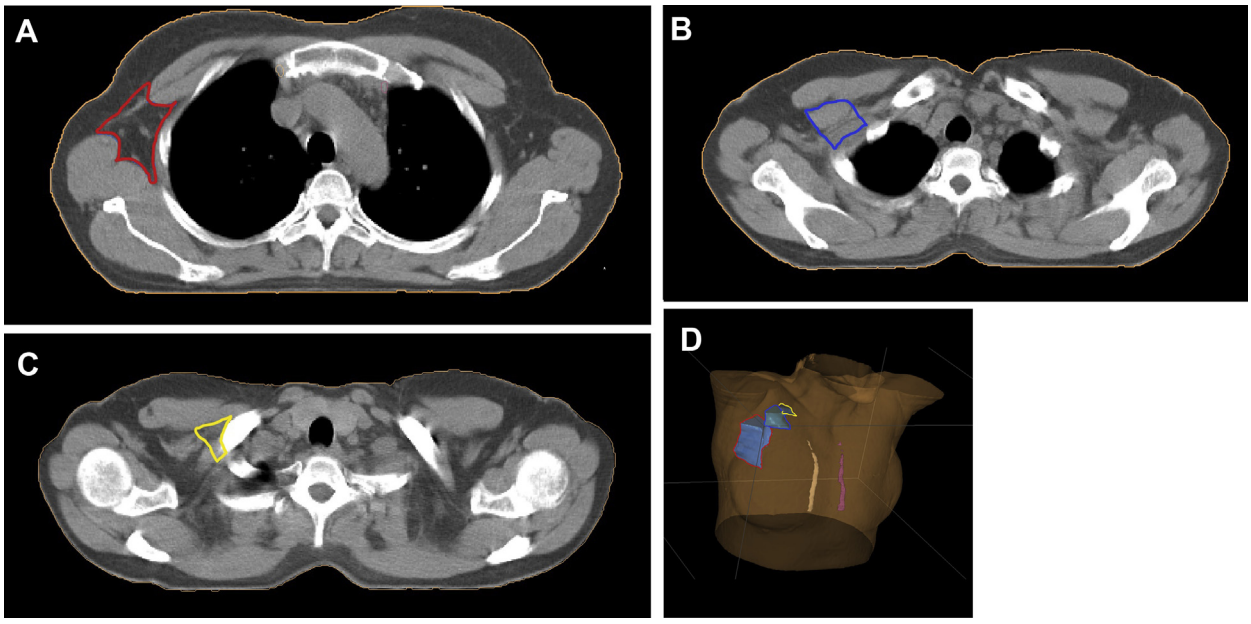

Fig. 2. Representative example of detailed radiation therapy planning record that was classified as receiving standard tangents with acceptable contouring of axillary levels I-III. A: contour level I (red); B: contour level II (blue); C: contour level III (yellow); D: contouring levels I-III (3D illustration).

Results

Of the 279 patients who were originally candidates for the central review process, 2 patients underwent secondary mastectomy after BCS with R1 resection, and 1 patient withdrew consent from the study. These 3 patients were excluded from all quality assurance review analyses.

The baseline characteristics of the remaining 276 patients are presented in Table 1. Unifocal tumors were diagnosed in 272 patients (98.6%), compared with 4 patients with multifocal disease (1.4%). All patients were clinically node-negative by palpation before BCS, with missing data in 6 patients. Two patients showed suspicious findings (0.7%) by axillary ultrasound; however, after negative axillary core biopsy or fine needle aspiration results, these patients were enrolled.

Central review revealed that only 235 radiation therapy planning records (85.1%) were delineated according to the INSEMA protocol. Major deviations regarding contouring were observed in 30 patients with SLNB (13.9%) and in 11 patients with no SLNB (19.6%). Despite repeated contact with the treating radiation oncologists, the record forms for 40 patients did not include contouring of the axilla levels, and poor quality of submitted records did not permit adequate review. One patient was also enrolled onto the HYPOSIB trial (Hypofractionation with SIB, NCT02474641) after BCS, which represents a major INSEMA protocol violation. These 41 cases were excluded from further analyses.

Among patients with protocol-compliant contouring (N = 235), minor deviations were detected by the reviewers in 9 cases (3.8%): 6 patients with SLNB (3.2%) and 3 patients with no SLNB (6.7%). Details of the minor deviations are listed in Table 2. Despite correct radiation therapy planning, 1 patient in the SLNB arm was not treated with postoperative WBI, resulting in 234 being available for complete central review analyses.

Radiation therapy techniques

The majority of INSEMA patients reviewed were treated with the 3D-CRT technique using standard tangential fields (n = 178, 76.1%). The remaining patients (n = 56) received modern IMRT techniques in variations such as step-and-shoot IMRT (n = 27, 11.5%), volumetric modulated arc therapy (n = 22, 9.4%), and tomotherapy (n = 6, 2.6%). The deep inspiration breath hold technique was applied in only 1 patient in the no-SLNB arm.

Conventional normofractionation was the preferred schedule for application of WBI in reviewed cases (n = 196, 83.8%), with minor differences between treatment arms (SLNB vs no SLNB: 81.5% vs 91.1%). Hypofractionation was used for 37 patients (15.8%), with a higher frequency in SLNB patients (17.9%) compared with patients with no SLNB (8.9%). Data on this aspect were missing for 1 patient.

Standard WBI values for PTV, dose median, and dose average are presented in Table 3. Considering a mixed population with normo- and hypofractionated schedules, all dose parameters are given as absolute and relative (percentage of prescribed breast dose) values. A tumor bed boost was delivered to 207 patients (88.1%), in the

Table 1 Baseline characteristics of 276 INSEMA patients selected for quality assurance review process

Parameter	n (%)
Age, y	
Mean	60.5
SD	10.3
Median	60.0
Range	36.0-83.0
≤50	56 (20.3)
>50	220 (79.7)
BMI, kg/m^2	
Mean	26.5
SD	5.3
Median	25.5
Range	17.7-46.5
<30	215 (77.9)
≥30	61 (22.1)
T stage by ultrasound and/or mammography (MRI optional)	
T1	252 (91.6)
T2	23 (8.4)
Missing	1
Histologic subtype	
Invasive-ductal	195 (70.7)
Invasive-lobular	30 (10.9)
Mixed ductal-lobular	7 (2.5)
Other	44 (15.9)
Grading (Elston and Ellis score)	
1	99 (35.9)
2	166 (60.1)
3	11 (4.0)
Hormone receptor status	
ER and/or PgR positive	273 (98.9)
ER and PgR negative	3 (1.1)
HER2 status	
Negative	265 (96.7)
Positive	9 (3.3)
Missing	2
Ki-67 proliferation marker	
≤20%	233 (88.3)
>20%	31 (11.7)
Missing	12

Abbreviations: BMI = body mass index; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; MRI = magnetic resonance imaging; PgR = progesterone receptor; SD = standard deviation.

majority of patients as SIB (144 patients; 69.6%). Nine patients (4.3%) were treated with intraoperative boost irradiation.

Dose distribution in axillary level I-III

Detected values for volumes, dose median, and dose average for each axillary level are shown in Table 4. To avoid different absolute doses between conventionally fractionated and hypofractioned cases, all dose parameters are presented as relative doses in percentage of prescribed breast dose. At least 25% of patients included in the analysis of "dose median" in axillary level I (based on the third quartile value [Q3]) were unintentionally treated with ≥95% of the prescribed breast radiation dose (47.88 Gy with normofractionation; 38 Gy with hypofractionation). Approximately 50% of reviewed INSEMA patients were irradiated with a median radiation dose of more than 85% of prescription dose in axillary level I. It should be noted that the extremely broad range (0.8%-110.5%) recorded for applied relative dose in level I resulted in high standard deviations for this analysis.

Table 2 Frequencies of minor deviations (delineation not in accordance with RTOG guidelines) in 9 patients (out of 235 with protocol-compliant contouring) with respect to axillary levels

Patient	Level I	Level II	Level III
#1		X	X
#2		X	
#3	X		
#4	X	X	
#5	X		
#6	X	X	
#7		X	
#8	X		
#9	X	X	X
Overall	6	6	2

Abbreviation: RTOG = Radiation Therapy Oncology Group.

Irradiated volumes and applied relative doses were significantly lower in axillary level II and III compared with level I values. However, 25% of patients (based on the Q3 value) still received a median radiation dose of ≥75% of prescription dose to axillary level II (37.8 Gy with normofractionation; 30 Gy with hypofractionation). In general, there were no differences between treatment arms in terms of the radiation dose applied to axillary levels. In all subanalyses, the values for the no-SLNB arm were equal to or lower than the values in the SLNB arm, reflecting the absence of intentional axillary overirradiation in the no-SLNB arm.

Factors influencing axillary dose distribution

Comparison with respect to obesity (body mass index [BMI] ≥30 kg/m^2) revealed significantly higher median axillary volumes in obese patients for level I (78 mL vs 54 mL, $P < .001$) and level III (19 mL vs 13 mL, $P < .001$); the difference for level II (23 mL vs 20 mL, $P = .205$) was not significant. Obese patients received a significantly higher radiation dose in level I, with a difference of approximately 9% relative dose (dose median: 92.5% vs 83.9%, $P = .026$; dose average: 79.5% vs 69.6%, $P = .018$). Delivered relative doses to level II (dose median:

Table 3 Standard values for WBI parameters regarding prescribed breast dose

	Treatment arms			
WBI parameter	SLNB (N = 184)	No SLNB (N = 45)	Rando2 directly (N = 5)	Overall (N = 234)
PTV, mL				
Mean	1032	1019	626	1021
SD	588	493	209	567
Median	903	852	604	878
Range	46-4038	256-2503	458-976	46-4038
Q1-Q3	620-1350	646-1384	472-621	619-1324
Missing				N = 2
Dose median, Gy				
Mean	49.5	50.9	51.4	49.8
SD	4.6	3.3	0.3	4.3
Median	50.8	50.9	51.3	50.9
Range	37.0-59.0	39.8-61.6	51.1-51.7	37.0-61.6
Q1-Q3	50.0-51.7	50.5-51.7	51.2-51.6	50.2-51.7
Missing				N = 7
Dose median (percentage of prescribed dose)				
Mean	102.0	102.6	101.9	102.1
SD	3.3	4.6	0.5	3.5
Median	101.3	101.2	101.8	101.3
Range	92.5-117.1	98.6-122.2	101.4-102.6	92.5-122.2
Q1-Q3	100.3-102.8	100.6-102.8	101.6-102.4	100.3-102.8
Missing				N = 7
Dose average, Gy				
Mean	49.1	50.9	50.3	49.4
SD	4.8	2.9	0.8	4.5
Median	50.4	50.6	50.7	50.4
Range	34.0-58.6	39.6-61.0	48.8-50.8	34.0-61.0
Q1-Q3	49.1-51.7	50.4-51.8	50.2-50.8	49.4-51.7
Missing				N = 4
Dose average (percentage of prescribed dose)				
Mean	101.4	102.2	99.7	101.5
SD	4.1	4.1	1.7	4.1
Median	100.6	101.0	100.6	100.7
Range	81.2-116.3	96.6-121.0	96.8-100.8	81.2-121.0
Q1-Q3	99.6-103.0	100.0-102.9	99.6-100.8	99.8-102.8
Missing				N = 4

Abbreviations: PTV = planning target volume; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SLNB = sentinel lymph node biopsy; WBI = whole-breast irradiation.

50.4% vs 12.0%, $P = .008$; dose average: 60.3% vs 27.5%, $P = .002$) and to level III (dose median: 5.6% vs 3.4%, $P = .01$; dose average: 11.2% vs 4.0%, $P = .003$) were significantly higher for patients with BMI $\geq$30 kg/m^2.

Hot spot analyses for axillary dose distribution were done with a special focus on obesity. In general, reviewed relative axillary maximal dose values for each level were not different between INSEMA treatment arms. Maximal relative dose parameters were not associated with obesity in level I ($P = .9$) but were significantly related to obesity ($\geq$30 kg/m^2 vs $<$30 kg/m^2) in level II (median maximal dose: 90.9% vs 29.4%; $P = .002$) and level III (median maximal dose: 87.6% vs 20.8%; $P = .005$). Defined hot spots (>120% prescription dose) were more frequently detected in axillary level I (n = 32; 14.0%) compared with level II (n = 3; 1.3%) and level III (n = 2; 0.9%). Hot spot frequencies in level I were not related to obesity ($\geq$30 kg/m^2: 14.6%; $<$30 kg/m^2: 13.8%).

Although all observed axillary volumes (significant difference only for level I, $P = .032$) were smaller in younger patients ($\leq$50 years), these patients were treated with nonsignificantly higher radiation doses in level I (dose median: 90.4% vs 83.6%, $P = .058$; dose average: 78.0% vs 69.6%, $P = .13$). No differences were seen for dose application in level II and level III with respect to age. The nonsignificant trend for higher axillary doses in level I among younger patients might be explained by higher frequency of boost application (100%) and conventionally fractionated radiation therapy (94.4%) compared with older patients (84.5% boost application, 80.1% conventional radiation therapy).

Table 4 Axillary dose parameters in INSEMA patients treated with postoperative WBI after BCS

	Treatment arms			
Parameter	SLNB (N = 184)	No SLNB (N = 45)	Rando2 directly (N = 5)	Overall (N = 234)
Axillary level I volume, mL				
Mean	67	71	65	68
SD	46	59	25	48
Median	56	56	69	56
Range	11-439	16-378	26-89	11-439
Q1-Q3	42-83	39-81	58-85	42-82
Missing				N = 6
Axillary level I dose median (percentage of breast dose)				
Mean	72.8	68.6	56.6	71.6
SD	31.4	30.6	44.2	31.5
Median	85.9	82.7	78.0	85.4
Range	1.3-110.5	0.8-99.0	5.4-94.6	0.8-110.5
Q1-Q3	54.8-96.6	42.5-95.1	12.1-92.9	50.4-96.0
Missing				N = 11
Axillary level I dose average (percentage of breast dose)				
Mean	68.9	64.6	47.4	67.6
SD	26.1	23.2	24.1	25.6
Median	74.2	68.4	48.2	72.3
Range	0.2-112.0	3.4-96.8	22.2-73.8	0.2-112.0
Q1-Q3	53.0-89.9	48.3-82.3	24.2-68.5	51.6-88.1
Missing				N = 8
Axillary level II volume, mL				
Mean	25	22	20	25
SD	19	13	7	18
Median	21	19	18	20
Range	2-151	1-70	14-33	1-151
Q1-Q3	15-29	13-28	17-18	15-29
Missing				N = 6
Axillary level II dose median (percentage of breast dose)				
Mean	39.9	29.7	20.7	37.5
SD	38.2	30.8	37.7	37.0
Median	20.8	13.2	6.4	14.9
Range	0.4-114.5	0.4-95.8	1.2-87.9	0.4-114.5
Q1-Q3	4.5-85.1	4.9-50.0	1.4-6.6	4.5-75.0
Missing				N = 11
Axillary level II dose average (percentage of breast dose)				
Mean	41.0	34.9	19.3	39.4
SD	32.6	26.4	24.7	31.5
Median	33.7	33.1	15.3	33.2
Range	0.5-114.8	0.4-95.6	1.4-61.5	0.4-114.8
Q1-Q3	10.3-69.6	7.6-54.9	1.4-17.1	9.5-64.9
Missing				N = 9
Axillary level III volume, mL				
Mean	18	15	13	17
SD	18	9	6	16
Median	13	13	13	13
Range	3-167	4-56	6-21	3-167
Q1-Q3	10-20	7-20	10-14	9-20
Missing				N = 6
Axillary level III dose median (percentage of breast dose)				
Mean	16.4	12.0	1.9	15.2
SD	27.1	21.5	1.4	25.9
Median	3.8	4.0	1.8	3.7
Range	0.1-105.8	1.1-87.1	0.6-3.8	0.1-105.8
Q1-Q3	2.1-12.1	2.4-6.0	0.6-2.8	2.2-7.7
Missing				N = 12

(*continued on next page*)

Table 4 (*continued*)

Parameter	Treatment arms			
	SLNB (N = 184)	No SLNB (N = 45)	Rando2 directly (N = 5)	Overall (N = 234)
Axillary level III dose average (percentage of breast dose)				
Mean	18.9	13.8	2.2	17.5
SD	26.2	20.1	1.6	25.0
Median	5.8	4.5	2.0	4.7
Range	0.3-105.0	0.2-84.7	0.6-4.0	0.2-105.0
Q1-Q3	2.3-25.2	2.7-15.5	0.8-3.6	2.3-21.0
Missing				N = 9

Abbreviations: BCS = breast-conserving surgery; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SLNB = sentinel lymph node biopsy; WBI = whole-breast irradiation.

The application of tumor bed boost showed no impact on delivered radiation dose in level I (dose median: 85.3% vs 86.7%, $P = .39$; dose average: 72.7% vs 67.9%, $P = .29$), level II (dose median: 20.8% vs 10.0%, $P = .061$; dose average: 34.7% vs 25.0%, $P = .052$), and level III (dose median: 3.7% vs 3.3%, $P = .23$; dose average: 5.0% vs 4.2%, $P = .15$). Significantly larger axillary volumes in level I were found with 3D-CRT when comparing modern radiation techniques (3D-CRT vs IMRT, $P = .025$). However, comparisons of axillary dose median or average with respect to radiation techniques consistently showed no statistically significant differences.

Finally, the fractionation schedule displayed an expected impact on axillary dose parameters when considering absolute values. Using relative dose values (percentage of prescribed breast dose), the delivered doses in all axillary levels were not different in patients treated with conventional fractionation compared with hypofractionation (level I: dose median 85.9% vs 84.2%, $P = .69$ [dose average 72.7% vs 69.7%, $P = .60$]; level II: dose median 20.8% vs 10.0%, $P = .31$ [dose average 36.5% vs 23.0%, $P = .20$]; and level III: dose median 3.7% vs 3.5%, $P = .39$ [dose average 5.0% vs 4.0%, $P = .33$]).

Discussion

Three European trials were designed to compare SLNB versus no axillary surgery in patients with clinically node-negative, early invasive breast cancer receiving BCS. The Italian SOUND (NCT02167490), German/Austrian INSEMA (both fully recruited), and ongoing Dutch BOOG 2013-08 (NCT02271828) trials focus on this question with different inclusion criteria and study aims. Hopefully, the results from nearly 8500 patients treated in these trials will be able to guide future axillary staging in BCS.

When reporting outcomes for standard versus reduced or no axillary surgery in patients with BCS, it is absolutely necessary also to include radiation therapy−related technical information.[19] After publication of results from the ACOSOG Z0011 trial,[20,21] it became clear that there had been no standardization of axillary radiation field angles and location of upper field borders of tangents.[22,23] A retrospective review of 228 detailed radiation therapy records from ACOSOG Z0011 patients (N = 891) by Jagsi et al[4] revealed a high incidence of protocol violations, with the use of high tangents and supraclavicular irradiation in a considerable number of patients. It is therefore impossible to discern how much of the axilla was irradiated in the Z0011 trial.[23]

Regarding the 276 patients who were analyzed in the central INSEMA review, 85% of the submitted radiation therapy planning records were protocol compliant and were of sufficient print/computer quality to permit review. In light of the very low rate of minor deviations (<4%) the data presented provide a comprehensive basis for discussion regarding currently preferred radiation therapy techniques and schedules. For the future, this will permit analysis of the treatment effect of incidental irradiation to the lower axilla with standard tangential fields.

The majority of the review population was treated with 3D-CRT (76.1%) and received WBI using a conventionally fractionated regimen (83.8%). Partial breast irradiation alone or prone techniques, in which substantially less axillary volume is irradiated, were not allowed in the INSEMA trial. A boost to the tumor bed is recommended in patients at higher risk of recurrence.[24] According to the long-term results of the European Organization for Research and Treatment of Cancer boost trial, “high risk” is defined by young age (≤50 years) and presence of ductal carcinoma in situ.[25] The rate of tumor bed boost was remarkably high (88%) among INSEMA patients for a cohort with median age of 60 years and other favorable prognostic factors (86% clinical T1 stage, 99% hormone receptor positivity).

Our review shows that with tangential breast irradiation, level I and II lymph nodes receive a relative median dose of 85.4% and 14.9%, respectively, for a prescription breast dose of 50 Gy or 40 Gy depending on preferred fractionation schedule. At least 25% of reviewed INSEMA patients were unintentionally treated with ≥95% of the prescribed breast radiation dose to level I. However, the optimal dose for curative radiation of metastatic disease in lymph nodes is currently unknown and might be

less than 95% of the prescribed breast radiation dose. Lower doses could result in a decreased therapeutic effect but might still be effective in subclinical, low-volume nodal disease.[26] In the concept of de-escalation in axillary surgery, incidental radiation dose takes on a more pivotal role, potentially moving from unintended to an intended dose of delivered irradiation.

The benefit of 3D radiation therapy includes more accurate irradiation of the targeted volume and reduced toxicity to surrounding tissue.[27] However, a reduced dose to the axilla might negate the potential benefit of incidental axillary irradiation and increase the risk of axillary recurrence in patients treated with BCS.[28,29] A previous retrospective study with 3D planning for WBI (N = 35) suggested that the proportion receiving 95% of the prescribed dose with standard tangents is 51% for level I and 26% for level II.[6] Van Roozendaal et al defined an elective radiation dose to the clip-marked SLNB site as at least 95% of the breast dose, as found in 32 of 42 included patients (76%) receiving 3D radiation therapy.[26] Kataria et al showed a relatively small, although significant, difference in the axillary radiation dose when comparing conventional 2D standard tangents with 3D-CRT or IMRT in a prospective evaluation of 50 cases.[7] The mean percentages of level I that received 90% of the breast dose were 73% for 2D radiation therapy, 57% for 3D-CRT, and 49% for IMRT; for level II, the mean percentages were 25%, 41%, and 35%, respectively. The small, but nonsignificant, differences between 3D-CRT and IMRT with respect to delivered axillary doses were confirmed by our analysis. In contrast, the incidental dose delivered to the axilla was significantly lower for IMRT compared with 3D-CRT in a preliminary study including 20 patients.[30]

In contrast to axillary levels, contouring of internal mammary nodes (IMNs) was not routinely done for INSEMA patients to detect incidental irradiation of IMNs. Using modern 3D-CRT and IMRT techniques, Song et al reported in a retrospective study median mean doses between 27.4 and 29.5 Gy in 84 patients with BCS for the IMN region not included in the PTV.[31]

Assuming $\geq$80% of the prescription breast dose as the optimal dose for curative radiation of low-volume disease in axillary lymph nodes,[32,33] approximately 50% of reviewed INSEMA patients received an adequate dose to level I, even with contemporary 3D techniques. The dose coverage was much less in axillary levels II and III, far below therapeutically relevant doses. The location of the tumor in the breast, the size of the breast, a left- versus right-sided lesion, a tumor bed boost, and BMI are sometimes cited as factors influencing the amount of radiation to the axilla.[26,34]

However, owing to limited case numbers, many trials have failed to demonstrate a relationship between these factors and the delivered axillary dose. Our analysis revealed a significant association between incidental radiation dose to the axilla and obesity (BMI $\geq$30 kg/m^2). Younger age ($\leq$50 years), boost application, and fractionation schedule (with respect to the relative dose) showed no impact on axillary dose distribution.

Gene expression assays are increasingly used for decision-making regarding adjuvant systemic therapy in early-stage, operable breast cancer.[35] There are some clinical situations in which there is also a need for predictive markers to better estimate the amount of benefit from adjuvant radiation therapy and surgery. To date, the available evidence on the possible predictive value of gene expression assays for radiation therapy or axillary surgery does not support their inclusion in the decision-making process.[36,37] Previously, the Memorial Sloan-Kettering Cancer Center developed a nomogram to predict the likelihood of a positive SLNB. This nomogram is a statistical approach for calculation of metastatic axillary risk by combining different histopathologic factors (plus age) and is still available online using Memorial Sloan-Kettering Cancer Center home page. Although validated by numerous centers, this nomogram is not a substitute for axillary SLNB.[2]

Our study has numerous strengths, including the preplanned, prospective, multicentric setting involving more than 100 radiation therapy facilities. Minor protocol deviations were within an acceptable range. However, our study also has a number of limitations. The percentage of incomplete or poor-quality records (15%) is suboptimal. Our review of planning records was restricted to the first 3 cases per radiation therapy institution, thus representing only a small subgroup (nearly 5%) of all recruited INSEMA patients. More than 80% of patients received conventionally fractionated radiation therapy, and the majority of patients also received the boost as SIB, which is still not widely accepted worldwide. All patients were treated in supine position, so results cannot be extrapolated to patients treated in prone position. Another limitation is that after trial recruitment started, a competing contouring consensus guideline was published by the European Society for Radiotherapy and Oncology (ESTRO).[38,39] Recently, a comparison of anatomic boundaries of contouring in the RTOG and ESTRO guidelines was presented by Gee et al.[40] Although the anatomic landmarks for contouring the axillary volumes are only subtly different between the guidelines, our data cannot be completely extrapolated to patients who were contoured following ESTRO recommendations. For RTOG, the inferior limit of level I is the pectoralis major insertion onto ribs, whereas ESTRO recommends the (typically more superior) fourth to fifth rib. ESTRO guidelines keep the superior border of level I inferior to that of RTOG to avoid irradiating the humoral head.[40]

Conclusions

Our central review yields first insights into contemporary radiation therapy techniques and schedules used and the extent of unintentional axillary radiation among selected

INSEMA patients with BCS. Collection and analysis of these data will also be available for the complete INSEMA population in the near future.

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