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Radiotherapy instead of axillary lymph node dissection: evaluation of axillary lymph node dose coverage with whole breast radiotherapy

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ABSTRACT

Background: The purpose of this study was to investigate the dose coverage of sentinel lymph nodes (SLN), level I, II and III axillary volumes from tangent fields for breast cancer patients with positive SLN without axillary dissection.

Materials and methods: In 30 patients with cN0 invasive breast cancer treated with breast conserving surgery and SLN biopsy, the SLN area was intraoperatively marked with a titanium clip. Retrospectively, the SLN area and axillary target volumes were contoured, and three plans [standard tangent fields (STgF), high tangent fields (HTgF), and STgF + axillary-supraclavicular field] were generated for each patient. The prescribed dose was standardized to 50 Gy in 2 Gy fractions to the isocenter.

Results: The mean dose with STgF or HTgF was 33.1 and 49.1 Gy ($p = 0.0001$) in the SLN area, 25.7 and 45.1 Gy ($p < 0.0001$) in the volume of level I, 7.2 and 28.9 Gy ($p < 0.0001$) in the level II and 3.5 and 12.7 Gy ($p = 0.0003$) in the level III. Adequate therapeutic doses to the level II or III volumes were delivered only with STgF + axillary-supraclavicular field. The mean dose of ipsilateral lung was the highest with the three-field-technique, 9.9 Gy. SLN area, level I, II or III were completely included in the HTgF with 93.3%, 73.3%, 13.3% and 0%, respectively.

Conclusions: SLN area should be marked by surgical clip and axillary target volumes should be contoured to obtain accurate dose estimations. The use of HTgF improve axillary coverage.

Key words: breast cancer; lymph nodes; lymph node dissection; radiation therapy

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Introduction

Recent clinical trials have shown that axillary lymph node dissection (ALND) provides no outcome benefit to N0 patients with limited sentinel lymph node (SLN) involvement who are treated with breast-conserving surgery (BCS) and whole-breast ± axillary-supraclavicular irra-

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diation [1, 2]. In the AMAROS trial, the 5-year axillary relapse with ALND or axillary-supraclavicular radiotherapy (RT) in N0 SLN positive patients was 0.43% and 1.19%, respectively [1]. However, the need of level III axillary-supraclavicular RT is unclear for patients with limited SLN involvement [3]. In the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial [2] the cumulative incidence of nodal recurrences at 10 years was 0.5% in the ALND arm and 1.5% in the SLN biopsy alone arm ($p = 0.28$). The ten-year cumulative locoregional recurrence with ALND or SLN biopsy alone was 6.2% and 5.3%, respectively ($p = 0.36$). The Saint-Gallen guidelines state that ALND should not be completed in N0 patients with one to two macro-metastases in the SLNs after BCS and tangential field (TgF) RT [4]. The American Society of Clinical Oncology (ASCO) updated guidelines recently concluded that women with one to two metastatic SLNs treated with BCS and TgF RT should not undergo ALND [5]. As the extent of axillary surgery decreases, the radiation dose to the axillary volumes becomes important for therapy planning. In the ACOSOG Z0011 trial dose distribution in the axillary volumes were not reported in the initial publication. Jagsi et al. [6] recently analysed RT dose coverage of ALN of that trial. Most patients treated in Z0011 trial received tangential RT alone, and some received no RT at all. Some patients received directed nodal RT via a third field. They concluded that further research is necessary to determine the optimal RT approach in patients with low-volume axillary disease treated with SLN dissection alone. The purpose of this study was to evaluate the dose distribution in the axillary volumes and critical organs using different field arrangements after BCS and SLN biopsy: standard tangent fields (STgF) ± axillary-supraclavicular field (ASF), and high tangent fields (HTgF) alone. The dose to SLN biopsy area, as determined intraoperatively by surgical clip, was also studied.

Materials and methods

This study included 30 women with clinically N0 invasive breast cancer who have undergone breast conserving surgery (BCS) and SLN biopsy between November 2015 and June 2017. During surgery, SLN area had been marked with a titanium clip. Following BCS all patients had 3D-conformal RT. During CT simulation the patients were positioned supine and immobilized with both arms raised above the head using a breast board. CT images with 5 mm slice thickness were obtained. The breast irradiation was planned with two opposing tangential fields with 6 MV photons. Standard tangential field margins were determined by palpation of the breast parenchyma with the addition of 1–2 cm margin in all directions. The superior borders of these fields intended to treat the breast only, without regard to nodal coverage. Approximately 2 cm (≤ 3 cm) of lung section was included in the posterior border of the field. In patients with SLN macro metastases, supraclavicular fossa field was also used to deliver an effective dose to the axillary apex and clavicular fossa. The supraclavicular fossa field was matched to the whole breast tangential fields. Patient and treatment characteristics are shown in Table 1. All procedures were carried out in compliance with the Declaration of Helsinki and conformed to the ethical standards of human experiments in our country, and all patients pro-

Table 1. Patient and treatment characteristics (n = 30)

Mean age, years (range)	60 (42–79)
Pathological tumor classification	
T1a	2
T1b	13
T1c	11
T2	4
Sentinel lymph node status	
pN0	25
pN1mic	1
pN1a	4
Estrogen receptor (ER) status	
ER-positive	28
ER-negative	2
Histologic grade	
Grade I	14
Grade II	13
Grade III	3
Radiotherapy parameter	
Standard fractionation (25 × 2 Gy)	9
Hypo-fractionation (15 × 2.67 Gy)*	21
With boost (10–18 Gy, 2 Gy/fraction)	9
Without boost	21

*for the study, treatments of all patients were planned with standard fractionation (25 × 2 Gy)

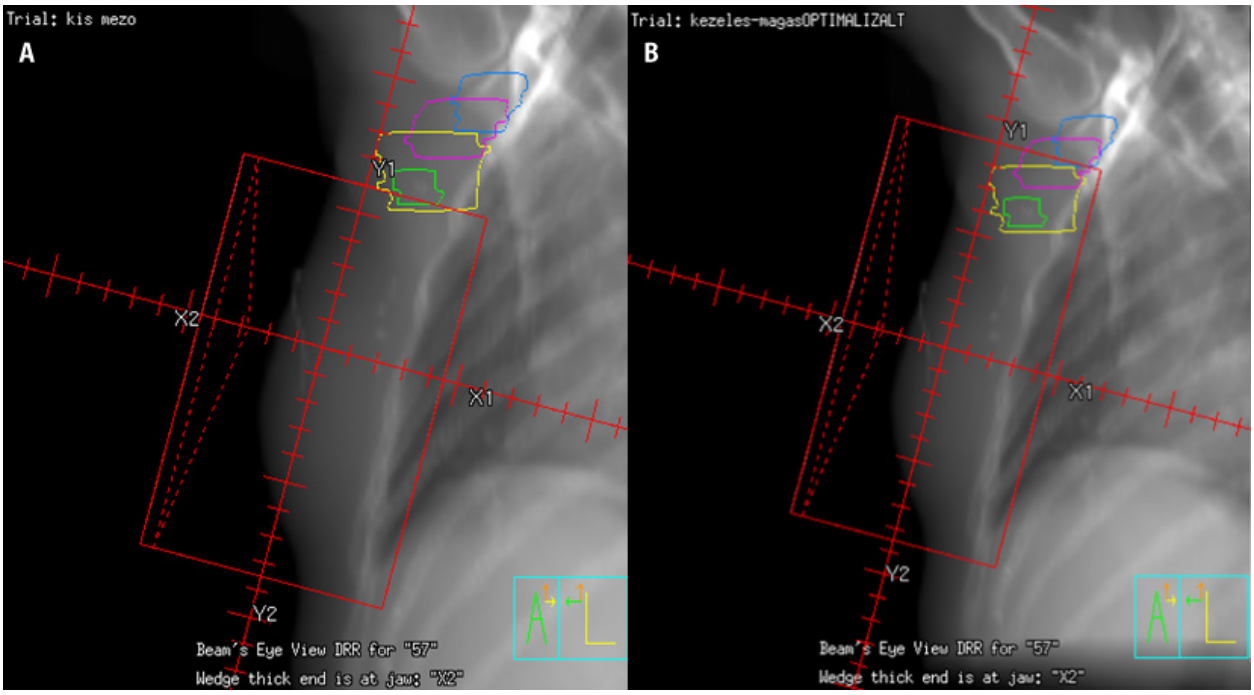

Figure 1. Coverage of the axillary volumes with standard (**A**) or high (**B**) tangent field (green line: sentinel lymph node clip area, yellow line: Level I volume, purple line: Level II volume, blue line: Level III volume). Sentinel lymph node area and Level I volumes are completely covered with high tangent field

vided written informed consent before the treatment. RT was given according to our institutional protocol, and retrospectively, for the purpose of this study, three plans were generated for each patient using the same CT data: irradiation via STgF, HTgF, and STgF + ASF. Axillary nodal volumes (SLN clip area, Level I, II and III) and organs at risk (heart and lung) were contoured using the Radiation Therapy Oncology Group (RTOG) contouring atlas [7]. The planning target volume was defined as the CTV (clinical target volume) plus a 5-mm expansion in all directions limiting to 5 mm below the external skin surface.

For analyses, STgF was defined with the superior border set at 2 cm below the humeral head, whereas HTgF consisted of a superior border placed at the inferior edge of the humeral head [8]. In the HTgF technique the field was also adjusted wider than the traditional standard field in the posterior direction to ensure inclusion of the axillary volumes, but the use of a wider field is limited by lung radiation dose constraint. The SLN clip area was defined as a volume of CTV with a 5 mm diameter surrounding the clip. For the purpose of the study, for all patients the prescribed dose to whole breast and axillary-supraclavicular fossa was standardized to 50 Gy in 2 Gy fractions in the isocenter. Mean doses were calculated to characterize the doses to the axillary volumes, heart (left-sided breast cancer only) and ipsilateral lung. Geometric coverage of the axillary volumes was classified according to the tangential field — planning target volumes (SLN biopsy area, level I, II and III) overlap: 100% overlap (complete coverage), < 100% overlap (partial coverage), 0% overlap (no coverage, target is out of field). Examples of coverage with a standard or a high tangent field are given in Figure 1. All comparisons of the mean doses were made using two-sided paired t-tests. The level of statistical significance was set at $p < 0.05$.

Results

The median number of removed SLNs was 2 (range 1–5). The mean volumes of level I, II or III were 45.34 cm^3 (range, 21.19–92.10 cm^3), 13.10 cm^3 (range, 5.79–39.01 cm^3) and 6.86 cm^3 (range, 2.60–15.18 cm^3), respectively. The SLN clip was below the level I volume in 1 case (3.3%), in the Level I volume in 28 cases (93.3%), and in the level II volume in 1 case (3.3%). The SLN most caudal or cranial position was located 5 cm be-

Table 2. Type of coverage of the axillary volumes in percentages (number) of patients by tangent fields

Coverage	SLN		Level I		Level II		Level III	
	STgF	HTgF	STgF	HTgF	STgF	HTgF	STgF	HTgF
Complete	53.3 (16)	93.3 (28)	6.7 (2)	73.3 (22)	3.3 (1)	13.3 (4)	0 (0)	0 (0)
Partial	30 (9)	6.7 (2)	73.3 (22)	26.7 (8)	13.3 (4)	73.3 (22)	0 (0)	33.3 (10)
None (out of field)	16.7 (5)	0 (0)	20 (6)	0 (0)	83.3 (25)	13.3 (4)	100 (30)	66.7 (20)

SLN — sentinel lymph node; STgF — standard tangent field; HTgF — high tangent field

Table 3. Doses in the axillary volumes and critical organs according to the field arrangement

Regions, organs	Mean dose [Gy] (range)				
Fields	STgF + ASF	STgF	HTgF	p-value (STgF *vs.* HTgF)	p-value (HTgF *vs.* STgF + ASF)
SLN_a	43.9 (12.8–51.4)	33.1 (2.4–50.8)	49.1 (45.1–55.8)	< 0.0001	0.0183
Level I	44.1 (29.0–49.1)	25.7 (1.7–48.3)	45.1 (24.1–54.5)	< 0.0001	0.4265
Level II	45.1 (34.5–53.5)	7.2 (0.9–45.9)	28.9 (2.8–48.8)	< 0.0001	< 0.0001
Level III	45.6 (21.7–56.6)	3.5 (0.6–34.8)	12.7 (1.7–45.0)	0.0003	< 0.0001
Lung*	9.9 (3.4–17.3)	6.6 (2.4–12.8)	8.0 (3.9–13.3)	< 0.0001	0.0043
Heart**	4.4 (1.7–10.9)	3.9 (1.6–6.2)	4.7 (1.9–8.0)	0.0083	0.5783

STgF + ASF — standard tangent field + axillary-supraclavicular field; HTgF — high tangent field; SLN_a — sentinel lymph node area; *ipsilateral lung; **left sided breast cancer

low the clavicle and 1 cm superior to the base of the clavicle.

The types and rates of geometric coverage for axillary volumes by tangential fields in patients are shown in Table 2. On simulation films, the rate of complete coverage for level I by HTgF or STgF was 73.3% and 6.7%, respectively ($p < 0.0001$). The rate of complete coverage with HTgF for level II or level III was 13.3% and 0.0%, respectively. Additionally, the rate of complete coverage for SLN clip area (SLNa) by HTgF or STgF was 93.3% and 53.3%, respectively ($p < 0.0001$). The HTgF was adjusted wider in 14 cases to improve coverage of Level I volume.

The mean doses delivered to SLNa, to level I, to level II and to level III with HTgF or STgF were 49.1 and 33.1 Gy ($p < 0.0001$), 45.1 and 25.7 Gy ($p < 0.0001$), 28.9 and 7.2 Gy ($p < 0.0001$) and 12.7 and 3.5 Gy ($p = 0.0003$), respectively. Using the three-field technique, the dose in the SLNa and level I was similar to the dose from HTgF (Tab. 3). The mean doses of critical organs are also shown in Table 3. The mean ipsilateral lung dose with HTgF or STgF was 8 Gy and 6.6 Gy ($p < 0.0001$). The mean lung dose was the highest with the three-field technique, 9.9 Gy. In the left-sided breast cancer patients ($n = 15$), the mean heart dose with HTgF or STgF was 4.7 Gy and 3.9 Gy, respectively ($p = 0.0083$). The mean heart dose with HTgF or STgF + ASF was 4.7 and 4.4 Gy, respectively ($p = 0.5783$).

The mean doses delivered to the 95% of axillary volumes from STgF or HTgF are shown in Table 4. The use of HTgF increased the doses significantly in all axillary volumes. The V20 (percentage volume received 20 Gy) for the lung with STgF, HTgF or STgF + ASF was 10.9%, 12.57% and 18.36%, respectively. Extended fields significantly increased the volume that received 20% of the prescribed dose (Tab. 4). The V30 (percentage volume received 30 Gy) for the heart with STgF, HTgF or STgF+ASF was 2.57%, 3.1% and 3.87%, respectively. Field ar-

Table 4. Dose coverage in the axillary volumes and critical organs according to the field arrangement

	D95 [Gy] (range)						V20 (%)	V30 (%)
	SLNa	Level I	Level II	Level III	Lung*	Heart**	Lung*	Heart**
STgF	24.9 (2.2–50.0)	7.6 (1.4–44.4)	3.4 (0.7–32.9)	1.9 (0.5–5.6)	0.5 (0.1–1.0)	1.4 (0.5–2.2)	12.1 (3.0–24.0)	2.8 (0.0–6.25)
HTgF	47.5 (32.3–51.3)	32.5 (3.3–49.5)	12.6 (2.0–47.3)	5.1 (1.1–40.0)	0.7 (0.3–1.4)	1.5 (0.7–2.5)	13.9 (5.0–25.0)	3.4 (0.0–6.25)
STgF + ASF	40.6 (5.0–51.0)	29.6 (4.4–48.1)	38.8 (10.0–46.7)	41.0 (5.3–52.1)	0.6 (0.1–1.1)	0.7 (0.4–1.3)	20.5 (5.0–41.3)	4.2 (1.0–17.5)
p-value STgF *vs.* HTgF	< 0.0001	< 0.0001	0.0043	0.0229	0.0032	0.0095	0.0124	0.0978
p-value HTgF *vs.* STgF+ASF	0.0076	0.3942	< 0.0001	< 0.0001	0.1042	< 0.0001	0.0002	0.4775

D95 — dose delivered to 95% of volume; V20 or V30 — volume received 20 Gy and 30 Gy; SLNa — sentinel lymph node area; STgF + ASF — standard tangent field + axillary-supraclavicular field; HTgF — high tangent field; *ipsilateral lung; **left sided breast cancer

Table 5. Correlation between geometric and dose coverage using high tangent field (HTgF)

Volumes	No*	Mean dose (range)	D95 mean (range)
SLN area	28	49.0 Gy (45.1–51.9)	48.1 Gy (38.6–51.3)
Level I volume	22	47.7 Gy (41.4–51.5)	42.5 Gy (22.5–49.5)
Level II volume	4	47.3 Gy (45.9–48.8)	45.1 Gy (43.5–47.3)

*number of cases with 100% overlap; SLN — sentinel lymph node

rangement had no significant impact on the V30 for the heart (Tab. 4).

The correlation between the geometric overlap with high tangent fields and the mean dose or D95 of target volumes was also studied in the cases of 100% overlap. Complete geometric coverage resulted generally in good dose coverage (Tab. 5).

Discussion

The locoregional control benefit of axillary treatment in invasive breast cancer was established first by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial, which randomized patients with clinically lymph node-negative disease to 1 of the 3 arms: radical mastectomy, total mastectomy with axillary irradiation, or total mastectomy alone without axillary treatment. Patients with an untreated axilla had a significantly greater risk of regional failure compared with those who either received axillary RT or underwent dissection, although no survival differences were observed between the groups. Surgery and RT were equally efficacious for axillary control. In the NSABP B-04 trial postmastectomy radiotherapy was delivered with the three-field technique, tangent and direct supraclavicular-axillary fields [9]. In the Z0011 trial [2] the whole breast irradiation was delivered with tangent fields and the supraclavicular-axillary field seldom was used. However, the risk of positive axillary nodes left behind is high for cN0 patients, treated only with SLN biopsy. In a randomized study from the National Institute of Oncology Budapest [10] the rate of positive axilla for clinically N0 patients, dissected following positive SLN biopsy, was 38.5%.

In the present study, we evaluated the coverage of axillary volumes and the dose of critical organs using three different RT field arrangements to irradiate clinically node negative breast cancer patients following SLN biopsy and BCS. There are some reports about the doses to the axillary lymph node region from postoperative whole-breast radiation, but the relationship between the SLN location and the whole-breast tangential field has not been sufficiently investigated. In our patients, during surgery the SLN area was marked with a titanium clip which is mandatory for accurate target volumes definition. The SLN clip was below the level I volume in 1 case (3.3%), in the level I volume in 28

cases (93.3%), and in the level II volume in 1 case (3.3%). In a multicenter validation study, the SLNs were found in level I in 89% of the patients [11]. In the study of Wadasaki et al. [12], the SLN locations were detected by SPECT/CT, and at 68 patients (98.5%) the SLNs were located in the level I region. In our cases, the SLN was located in most caudal or cranial position at 5 cm below the clavicle and 1 cm superior to the base of the clavicle, respectively. In the study of Rabinovitch et al., these distances were 6.5 cm and 1.5 cm, respectively [13]. Zunino et al. [14] intended to irradiate the breast only and the SLN clip was covered by the tangent fields in 61% of the cases. In our patients the SLN clip area was completely covered with STgF or HTgF in 53.3% (16/30) and 93.3% (28/30) of the cases. In the study of Belcacemi et al. [15], radiation therapy was planned to treat the breast alone and 38% of the SLN clips were inside the tangent fields. Rabinovitch et al. [13] used STgF and 78% of the SLN clips was completely within the treated breast fields. In the prospective evaluation of Belcacemi et al., SLN biopsy area was completely covered by the TgF in 12 of 25 patients (48%), independently of the TgF size, but HTgF was used only in five patients [8]. In their study, the use of HTgF instead of STgF significantly increased the mean dose of axillary volumes, SLN area: 45 Gy *vs.* 30 Gy and level I volume: 38 Gy *vs.* 22 Gy. These results are close to our findings, SLN area: 49 Gy *vs.* 33 Gy ($p < 0.0001$) and level I: 45 Gy *vs.* 26 Gy ($p < 0.0001$). In another analysis of Belcacemi et al. [15], the mean dose of level I volume with STgF or HTgF was 20 Gy and 33 Gy, respectively ($p < 0.0001$), but the mean dose of level II volume was only 11 Gy and 4 Gy ($p = 0.002$). They concluded that the tangential fields can allow only a limited coverage of the axilla. In our patients, the mean dose of level II volume was somewhat higher: with HTgF or STgF 29 Gy and 7 Gy, respectively ($p < 0.0001$), but the geometric coverage of level II volume by HTgF was complete only in four patients. Aguiar et al. [16] intended to treat only the breast and the mean doses of level I, II or III were 43.9 Gy, 38.6 Gy and 19. 5 Gy, respectively. Higher doses were associated with the more voluminous and pendulous breasts. Csenki et al. [17] used only STgF to treat the whole breast and the mean dose of Level I, II or III volumes were 37.7 Gy, 13.8 Gy and 1.6 Gy, respectively. In both studies the conclusion was that axillary coverage with whole breast radiotherapy seems to be insufficient. Mayinger et al. [18] compared helical Tomo Therapy (TT) with 3D conformal conventional tangent field RT. TT improved dose coverage of level I but it was not efficient (TT or 3D conformal RT mean dose: 31.6 Gy and 24.0 Gy, respectively).

It is estimated, that using STgF, more than 50% of level I and 20% to 30% of level II nodes receive 95% of the prescribed radiation dose. This is dependent on patient anatomy and where the radiation oncologist sets the upper border of TgF [3]. Nagar et al. [19] evaluated 30 patients and the D95 (dose to 95% of volume) received by level I and level II volumes increased from 16.38 Gy and 5.71 Gy for STgF, to 49.38 Gy and 48.08 Gy for HTgF, respectively. The modified tangent fields resulted in a very good dose coverage but the borders of HTgF were not defined exactly. They stated: "Tangent treatment fields were modified to include Ax1 and Ax2 to 95% of the prescribed dose". In our patients the HTgF was also adjusted wider in 14 cases to improve coverage of level I volume. Therefore, the use of the modified tangent field technique is more exact definition than the high tangent field technique. In the study of Alco et al. [20], HTgF was simulated for 30 patients. The mean D95 for level I or level II was 16.79 Gy and 11.59 Gy, respectively. They concluded, that HTgF do not adequately cover the level I and II axillary lymph node regions. In our study the mean D95 even with HTgF was also insufficient: in level I or level II 29.08 Gy and 11.20 Gy, respectively.

We also studied the geometric coverage of axillary target volumes with tangent breast fields. The geometric coverage was very insufficient with STgF, but the use of HTgF improved the results significantly. The rate of complete coverage of SLNa, level I, II or III volumes was 93.3%, 73.3%, 13.3% and 0%, respectively. Our results show that the complete coverage of level II volume even with modified tangent field is very poor.

Variability in contouring the targets between the institutions is substantial but level II volume shows lower variation. In our patients the mean value of level II volume was 13 cm^3 and in the studies using RTOG Atlas, the mean values were also under 20 cm^3 [16, 17, 20]. Nodal target volume definition in breast cancer radiotherapy using RTOG or European Society for Radiotherapy and Oncol-

ogy (ESTRO) atlas has been debated [21, 22]. We used the RTOG atlas due to the earlier introduction and the available published results. In early breast cancer, ESTRO guidelines have been preferred recently because of the improved coverage of the upper part of the axilla. Independently of the contouring methods, the dose of upper axilla from tangent breast fields is not sufficient.

In the study of Nitche et al. [23] the use of HTgF significantly increased the mean heart dose: STgF or HTgF 3.9 Gy and 4.7 Gy, respectively. In our patients the mean values were also 3.9 Gy and 4.7 Gy ($p = 0.0083$). In the study of Alco et al. [20] the tangential field was shaping with multi-leaf collimators according to axillary level volumes. This technique increased the mean lung dose significantly, with HTgF or multi-leaf collimators HTgF: 6.5 and 9.6 Gy, respectively ($p < 0.0001$). In our patients the mean lung dose was 8.0 Gy (range: 3.9–13.3 Gy) with HTgF and the three-field technique further increased the mean lung dose: 9.9 Gy (range: 3.4–17.3 Gy). Using modified tangential irradiation technique, the lateral border of the field is also extended laterally to include the level I and II axillary lymph nodes. Ohashi et al. [24] stated that the deep tangential field increases the lung dose. In our study the use of HTgF also increased significantly the doses to the lung and heart compared with STgF irradiation. At our patients the use of the three-field technique increased both mean lung dose and V20 of the lung compared with tangent field RT. Haffty et al. [3] stated that lymph nodes in the level III/supraclavicular region are believed to be at risk when four or more positive nodes and one to three positive nodes in selected high-risk patients are detected at ALND. They recommend the use of ASF only for patients with high risk (three SLNs positive, primary tumor 3–4 cm, lympho-vascular invasion is present, ER negative cancer). Tangent field RT and systemic therapy provide good locoregional control for low risk cN0 patients with 1–2 positive SLN, in spite of the inadequate dose coverage of level I–II regions [2]. In the propensity score matching analysis of BIG02/98 and BCRG005 trials regional nodal irradiation (RNI) did not improve outcomes [25]. However, in these trials RNI was given after ALD and the target volume was the anatomic site of the dissected axillary lymph nodes. Following SLN biopsy without axillary dissection the target volumes are the undissected lymph nodes with risk of metastases.

Conclusions

For women with SLN positive breast cancer in whom primary RT is used to treat the axilla, the knowledge of the axillary anatomy is necessary for a proper design of the tangential field borders. To understand the impact of that stipulation, it is necessary to understand the anatomic relationship of the axillary lymph nodes to the tangential RT fields used for treatment of the breast. It is important to underline that due to the paradigm shift, the target volumes are the undissected lymph nodes with risk of metastases and not the dissected axilla. Without studying the dose coverage in the accurately contoured axillary target volumes, the unresolved issues (how axillary dose coverage affects endpoints, such as axillary recurrence, locoregional failure, pulmonary toxicity and distant metastasis) cannot be answered. In terms of coverage of SLN region and level I axilla, the use of modified (extended) tangent field instead of the three-field technique, seems to be an appropriate treatment only for selected low risk SLN positive cN0 patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Statement of ethics

The paper is exempt from ethical committee approval, because the patients received their treatment according to our clinical protocol, and the treatment planning evaluation was carried out retrospectively.

Author contributions

B.B., J.F., T.M.: substantial contributions to conception and design, drafting of the manuscript, performing statistical calculations; Z.Z., D.M.: revision of radiotherapy planning; C.P., T.M., Z.M., B.D.: critical revision for important intellectual content.

Data availability statement

All data generated or analyzed during this study are stored locally at our institution and are available on request.

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