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Mapping of the functional anatomy of lymphatic drainage to the axilla in early breast cancer: A cohort study of 933 cases

Bence Dorogi [a, *, 1], Bence Bukovszky [b], Tamás Mátrai [a], Ákos Sávolt [a], Csaba Polgár [c, d], Péter Kelemen [a], Tibor Kovács [e], Ferenc Rényi-Vámos [f, g], Gabriella Ivády [h], Eszter Kovács [i], Melinda Téglás [j], Miklós Kásler [k], Zoltán Mátrai [a]

[a] Department of Breast and Sarcoma Surgery, National Institute of Oncology, Ráth Gy. u. 7-9, 1122, Budapest, Hungary
[b] Centre of Radiotherapy, National Institute of Oncology and Department of Oncology, Semmelweis University, Ráth Gy. u. 7-9, 1122, Budapest, Hungary
[c] Centre of Radiotherapy, National Institute of Oncology, Ráth Gy.u. 7-9, 1122, Budapest, Hungary
[d] Department of Oncology, Semmelweis University, Ráth Gy. u. 7-9, 1122, Budapest, Hungary
[e] Department of Breast Surgery, Guy's and St Thomas's Hospitals NHS Foundation Trust, Great Maze Pond, London, SE1 9RT, United Kingdom
[f] Thoracic Surgery Department, National Institute of Oncology, Ráth Gy.u. 7-9, 1122, Budapest, Hungary
[g] Thoracic Surgery Clinic, Semmelweis University, Ráth Gy.u. 7-9, 1122, Budapest, Hungary
[h] Department of Molecular Pathology, National Institute of Oncology, Ráth Gy. u. 7-9, 1122, Budapest, Hungary
[i] Department of Diagnostic Radiology, National Institute of Oncology, Ráth Gy. u. 7-9, 1122, Budapest, Hungary
[j] Department of Nuclear Medicine, National Institute of Oncology, Ráth Gy. u. 7-9, 1122, Budapest, Hungary
[k] National Institute of Oncology, Ráth Gy. u. 7-9, 1122, Budapest, Hungary

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ARM
Axillary reverse mapping
ALND
Axillary lymph node dissection
BCS
Breast-conserving surgery
HTgF
High tangential fieldRT
Radiotherapy
SLN
Sentinel lymph node
SLNB

ABSTRACT

Introduction: The aims of this study were to investigate the correlation between lymphatic drainage and the sentinel lymph node (SLN) status of the subregions in the context of the clinic-pathological parameters of the tumour and the coverage of the axillary volumes by standard and high tangential fields (STgF and HTgF) for whole breast radiotherapy and axillary reverse mapping (ARM).
Patients and methods: 933 women with early breast cancer and clinically negative axillary status underwent breast surgery and SLN biopsy followed by axillary lymph node dissection in SLN-positive cases. The subregional localisation of the SLN(s) was registered and statistically analysed with the clinic-pathological characteristics of the breast tumour. In node-positive patients treated with breast-conserving therapy in whom the SLNs were found in the anterior or posterior axillary subregions, the axillary volumes were contoured using the Radiation Therapy Oncology Group contouring atlas (n = 61).
Results: In 91.1% (n = 797) of the cases, the SLN appeared in the anterior, posterior or central subregions. Using HTgF, Level I or II were completely covered in 65.6% (40/61) and 6.6% (4/61) of the cases, respectively. With STgF, the complete coverage was 0% for both levels.
6.8% (n = 63) of all cases had one positive lymph node in the expected ARM lymph node regions.
Discussion: A SLN is more than likely to be present in the anterior, posterior and central axillary subregions. Tangential fields allow only limited coverage of the axillary volumes. Preserving the lateral subregion during ARM may increase the possibility of understaging.

* Corresponding author. Department of Breast and Sarcoma Surgery, National Institute of Oncology, Ráth Gy. u. 7-9, 1122, Budapest, Hungary.
E-mail addresses: Dorogibence@gmail.com (B. Dorogi), bence.bukovszky@gmail.com (B. Bukovszky), tamas.matrai@hotmail.com (T. Mátrai), drsavolt@hotmail.com (Á. Sávolt), polgar@oncol.hu (C. Polgár), dr.kelemenp@gmail.com (P. Kelemen), tiborkovacsdr@yahoo.co.uk (T. Kovács), ferenc.renyi-vamos@meduniwien.ac.at (F. Rényi-Vámos), ivadygabi@oncol.hu (G. Ivády), koveszt5@gmail.com (E. Kovács), teglas@oncol.hu (M. Téglás), m.kasler@oncol.hu (M. Kásler), matraidoc@gmail.com (Z. Mátrai).
[1] Present address: Department of Surgery Polyclinic of Hospitaller Brothers of St. John of God Frankel Leó út 17–19., 1027 Budapest, Hungary.

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Sentinel lymph node biopsy
STgF
Standard tangential field
WBI
Whole breast irradiation
na
Not applicable

Introduction

Regional lymph node status is one of the most important prognostic factors for disease-free and overall survival in breast cancer [1–5]. Today, the gold-standard method for staging patients with early-stage breast cancer with clinically negative axillary lymph nodes is the sentinel lymph node biopsy (SLNB) [4,5].

To optimise the effectiveness of SLNB, the precise pre- and intraoperative mapping of lymphatic drainage is mandatory [4–6].

Anatomically, the axillary region is divided into five subregions: anterior, posterior, lateral, central and apical zones [7] (Fig. 1).

The anterior subregion is located under the lateral edge of the pectoralis minor muscle along the lateral thoracic vein. The posterior zone is found adjacent to the posterior wall of the axilla along the thoracodorsal nerve and vessels. The lateral subregion is located close to the lateral wall of the axilla, in relation to the proximal part of the axillary vein. The lymph nodes in this zone receive the vast majority of the efferent lymph vessels of the upper limb. The central zone is in the middle of the pyramid-shaped space of the armpit, close to the base of the axilla. The apical subregion is found in the apex medially to the distal part of the axillary vein.

These subregions correspond to the axillary node levels previously described by Berg [8]. The anterior, posterior and lateral subregions constitute Level I, the central zone forms Level II and the apical zone constitutes Level III [7].

Clear relationships between the anatomic location and metastatic status of the SLN have been revealed [9,10]. Histologically positive SLN was detected in Level I in 96% of cases and in Level II in 4% of cases by SPECT/CT [10].

A better understanding of the relationships between the subregional drainage pattern of SLN, the subregional localisation of SLN and the correlation to location and pathological characteristics of the primary breast tumour could have particular importance in determining whether ALND can be safely omitted.

The ACOSOG Z0011 trial did not perform ALND for early-stage breast cancer patients with 1–2 metastatic SLNs (cT1-2, pN1), and in the majority of the patients, the axilla was treated only with tangential field irradiation following breast-conserving surgery (BCS). After a median follow-up of 9.3 years, the data compared to the traditional ALND group showed no differences in local recurrence-free survival [11,12]. However, in the ACOSOG Z0011 trial, dose distribution in the axillary volumes was not reported in the initial publication. Jagsi et al. [13] recently analysed the radiotherapy (RT) coverage of the axillary lymph nodes of that trial. Most patients treated in the Z0011 trial received tangential RT alone, and some received no RT at all. Some patients received directed nodal irradiation 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 SLNB alone.

A recent surgical technique that is less radical and therefore decreases the morbidity of SLNB and ALND, especially lymphedema, is ARM [14–16]. The lymphatic drainage of the upper limb that runs through the axilla - most often the lateral subregional lymphatic structures - is identified by injecting radioisotope or blue dye to the ipsilateral limb subcutaneously, and these nodes are spared during the operation, removing only the lymph nodes that drain the lymph of the breast. The technique was proven to be feasible with a low level of evidence; however, the question of oncological radicality still arises due to the uncertainty of the metastatic status of the ARM lymph nodes that are not removed [17].

We sought to determine whether there is a correlation between the lymphatic drainage and the SLN status of the subregions. Our main objectives were as follows:

- To examine the location of the SLN in the axillary subregions in a representative cohort of patients with early-stage breast cancer.
- To assess statistical correlations between the clinicopathological characteristics of the primary breast tumour and the subregion of the SLN.
- To analyse the subregional localisation of metastatic SLNs.
- To assess the statistical correlation between axillary subregions outside the tangential and extended tangential RT coverage field applied in the ACOSOG Z0011 trial and the SLN positivity within these subregions after BCS.
- To study the axillary coverage with STgF or HTgF irradiation in node-positive patients.
- To assess the SLN positivity rate in the lateral, unremoved subregion when the ARM technique is applied.

Patients and methods

A retrospective cohort study was performed between March 2013 and February 2015. 933 female patients older than 18 years were enrolled with primary unilateral invasive or microinvasive, clinically lymph node-negative early-stage breast cancer (clinically $T \leq 5$ cm, N0M0). Exclusion criteria included previous ALND, cN1-2, pregnancy, lactation and necessity of neoadjuvant treatment for breast cancer [18,19].

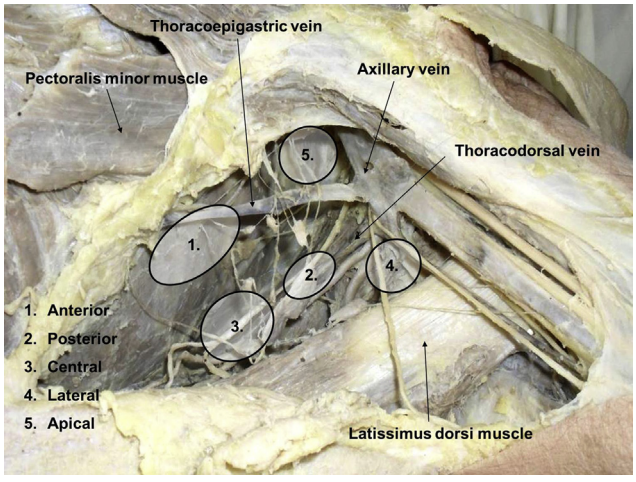

Fig. 1. Subregions of the axilla (left side, human cadaveric dissection).

The complex oncological therapy was performed according to the actual international guidelines [18–20] adopted by the National Institute of Oncology and was not different from those who were not included in the trial. Radiopharmaceutical (80 Mbq ^{99m} Tc labelled nanocolloid, particle size: 50–800 nm) was injected to the intratumoural area or periareolar tissue on the day before surgery. If the lymphoscintigraphy was unsuccessful, 2–3 ml of periareolar Patent blue 25 mg/ml® dye injection was applied 10 min before the operation.

Patients then underwent a wide excision or mastectomy and axillary SLNB followed by ALND instantly if the SLN was positive by intraoperative imprint cytology or as a second operation if the SLN was positive only by histological examination. If isolated tumour cells or micrometastases were found in the SLN (n = 33), ALND was omitted.

The subregional localisation of the SLN(s) was identified and recorded on a standardised data sheet by the operating surgeons immediately after biopsy in the operating theatre (Fig. 1). The harvested SLNs were separated and labelled with their localisation for pathological processing. Imprint cytology was performed intraoperatively, and if the result was positive, the operation was completed with ALND. Postoperatively, all the removed lymph nodes were meticulously examined by the pathologists according to the guidelines [21,22]. In cases of false negative SLNB, the subregional localisation and the number of metastatic lymph nodes left behind in the axilla could not be identified by our applied methods.

Following BCS, all patients had 3D-conformal RT. Patients were placed supine with both arms up and both hands holding on to a support during CT simulation. CT scan images with 5-mm sections were obtained. The breast was irradiated with two opposing tangential fields with 6 MV photons. STgF margins were determined by palpation of the breast parenchyma with the addition of a 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 (max. 3 cm) of the lung was included in the posterior aspect of the field. In node-positive patients, an additional field was also used to deliver an effective dose to the axillary apex and clavicular fossa. The total dose of the whole breast and supraclavicular fossa was 50 Gy (25 × 2 Gy). Breast irradiation was given via STgFs. The STgF upper margin was generally the base (±1 cm) of the clavicle. Retrospectively, for the purpose of this study in 61 randomly selected node-positive patients treated with breast-conserving therapy in whom the SLNs were found in the anterior or posterior axillary subregions (Level I), HTgFs were simulated using the same CT data. HTgF consisted of a superior border placed at the inferior edge (or below maximum 2 cm) of the humeral head. Before RT planning, axillary volumes (Levels I, II and III) were contoured using the RTOG (Radiation Therapy Oncology Group) contouring atlas [23]. Coverage of the axillary volumes by tangential fields was classified according to the tangential field-planning target volumes (Levels I, II and III) overlap: 100% overlap (complete coverage), <100% overlap (partial coverage), and 0% overlap (lack of coverage: out of field). Examples of coverages are given in Fig. 2.

The study was approved by the institutional ethical committee board and was registered on Clinicaltrials.gov (identifier: NCT01804309).

The clinical trial did not alter the lege artis oncological treatment and SLN intervention in any way.

All the collected data were registered in the institutional database and statistically analysed using Fisher's exact test. P-values less than 0.05 were considered statistically significant. Statistical analysis was performed using Statistica 12.0 software (StatSoft, Tulsa, OK) or PAST version 1.86b [24].

Results

A total of 933 women were enrolled in the study. The mean age of the patients was 64.1 years (range 19–91 years, median: 64 years). Three women were excluded because the breast tumour was larger than 5 cm according to the postoperative pathologic examination. Another two patients were ruled out due to newly discovered lympho-proliferative disorders affecting the axillary lymph nodes. Another 58 patients were discarded because of an uninterpretable sentinel data sheet or incomplete clinical-histological data.

The detailed pathologic characteristics of the primary breast tumours are summarised in Table 1.

Regarding the location of the breast cancer, 44.7% (n = 417) were in the upper-outer, 14.7% (n = 137) in the upper-inner, 9.9% (n = 93) in the lower-outer, 6.7% (n = 63) in the lower-inner quadrant, and 2.8% (n = 27) in the axillary process (tail of Spence); 12.8% (n = 119) were central tumours and 3.5% (n = 33) were multiplex.

There was a significant correlation between the location and the molecular subtype of the tumour (p = 0.022). Non-luminal tumours were mainly localised in the upper quadrants (84.6% n = 11).

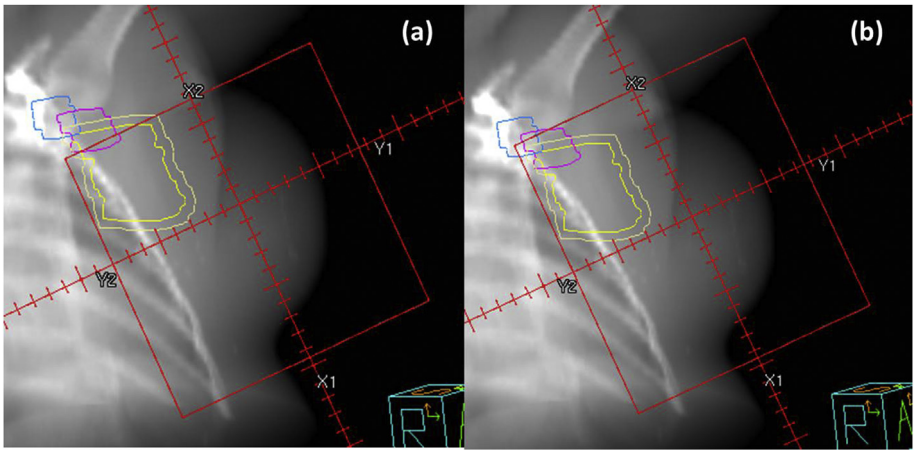

Fig. 2. (a) Coverage with standard tangential field (red square). Yellow lines = Level I volumes: inner line - clinical target volume; outer line - planning target volume; partial coverage. Purple line = Level II clinical target volume; partial coverage. Blue line = Level III clinical target volume; no coverage, out of field. (b) Coverage with high tangential field (red square). Yellow lines = Level I volumes: inner line - clinical target volume; outer line - planning target volume; complete coverage. Purple line = Level II clinical target volume; partial coverage. Blue line = Level III clinical target volume; partial coverage.

Similarly, the triple negative subtype was also likely to appear in the upper-outer quadrant (57.1%; n = 40). However, cancers in the lower-inner quadrant were mostly Her2-enriched (17.1%; n = 7). [Table 2.].

The tracer for lympho-scintigraphy was injected intratumorally and periareolarly in 38.8% (n = 362) and 57.6% (n = 537) of the cases, respectively. We used only radiopharmaceutical (80 Mbq ^{99m}Tc labelled nanocolloid) in 86.9% (n = 811), Patent blue dye in 4.4% (n = 41) and both in 4.8% (n = 45) of the cases.

None of the examined characteristics of the primary breast cancer (molecular subtype p = 0.360) had significant correlation with the subregional localisation of the SLN.

We divided our study population into two groups based on the injection site and analysed the relationships between the location of the SLN and location of the primary breast tumour. In case of intratumoural application, we found significant correlation between the location of the breast cancer and the subregional location of the SLN (p = 0.016). However, examining only the histologically positive SLNs, the relationship between their location and the primary tumour location was not statistically significant (p = 0.674).

If periareolar injections were used, the location of the SLN was not dependent on the location of the primary breast tumour (p = 0.398), whilst the correlation between the location of the positive SLN and the location of the breast cancer was statistically significant (p = 0.039). [Table 3.].

According to our data, tumours in the upper-outer quadrant are least frequently drained to the anterior subregion (34.2%). Posterior subregion receives lymph mainly from the upper-outer quadrant (31.6%) and the axillary process (36.3%), whereas the inner and central quadrants have very similar drainage patterns with a tendency to give efferent lymphatics more often to the anterior (53.9%, 69.6% and 54.5%) and central (28.8%, 26.1% and 22.7%) lymph nodes. The central lymph nodes receive lymphatic drainage equally from the different quadrants of the breast [Table 3.].

An average of 1.6 (range: 1–8, median: 1) SLNs were harvested per operation, and the SLN positivity rate was 20.3% (n = 189).

We also analysed the distribution pattern and metastatic status of the SLN in the subregions of the axilla [Table 3.]. The most common site of the SLN was the anterior subregion (39.9%; n = 349), while the least common was the apical subregion (3.4%; n = 30). In contrast, the positivity rate was higher in the apical subregion (30.0%; n = 9) than in the anterior subregion (20.9%; n = 73). The SLN was present in the lateral subregion in 5.5% (n = 48) of the cases. Of these 48 lymph nodes, 11 SLNs - 1.3% of the total cases - were positive. In the central and posterior subregions, 53 (6.1%) and 43 (4.9%) SLNs, respectively, were found to be positive out of the 245 (28.0%) and 203 (23.2%) removed lymph nodes, respectively.

In 91.1% (n = 797) of the cases, the SLN appeared in the anterior, posterior or central subregions, corresponding to Level I and II zones [Table 3].

In 503 patients, the SLN was located within the anterior or posterior subregion (Level I). 111 of them (22.1%) had axillary lymph node metastasis, and 83 (16.5%) of them were treated with RT in our Institute. Sixty-one women were subjected to WBI. The coverage of axillary volumes by tangential fields is given in Table 4. There was a significant difference between the two plans regarding the coverage of the Level I axillary volume. HTgF increased the rate of complete coverage from 0% to 65.6% (40 of 61; p < 0.0001). Concerning the Level II volume, the rate of complete coverage with STgF or HTgF was 0% and 6.6% (4 of 61), respectively (p = 0.1198). The rate of "out of field" cases was very high with STgF, 72.1% (44 of 61), but "out of field" cases were not observed with HTgF irradiation (p < 0.0001). The coverage of the Level III volume was very poor

Table 1
Pathological characteristics of the primary breast tumour.

pT	n	%
pTis	104	11.8
pT1mi	3	0.3
pT1a	31	3.5
PT1b	95	10.8
pT1c	316	36.0
pT2	300	34.1
pT3	30	3.4
Grade (invasive tumours)		
I	180	23.4
II	370	48.1
III	219	28.5
Grade (in situ carcinomas)		
Low	28	26.9
Medium	50	47.8
High	26	25.3
Receptor status		
ER	751	80.5
PR	641	68.7
Her2	72	7.7
Molecular subtype		
Luminal A	438	59.4
Luminal B	171	23.2
Luminal B-Her2+	41	5.6
Non-luminal	73	9.9
Triple negative	14	1.9
Lymphovascular invasion		
Present	322	39.3
Not present	497	60.7
Histological type		
Invasive ductal carcinoma	643	73.1
Invasive lobular carcinoma	99	11.3
Other invasive	34	3.9
DCIS	75	8.5
LCIS	16	1.8
Other in situ	13	1.5
Palpability		
Palpable	499	55.9
Not palpable	393	44.1
Mitotic activity		
<11	539	67.0
11–20	157	19.5
20<	109	13.5
Type of breast surgery		
Mastectomy	371	39.8
Breast conserving surgery	562	60.2
SLN positivity		
SLN-negative patients	744	79.7
SLN-positive patients	189	20.3
Total removed SLNs	1538	na
SLNs removed per operation	1.6	na
ALND		
Total number of ALND	156	16.7
Total number of removed lymph nodes	2109	na
Lymph nodes removed per ALND	13.5	na
Positive lymph nodes per ALND	406	19.3

Table 2
Correlation between molecular subtype (column) and the location (row) of the primary breast tumour (p = 0.022).

	Luminal A		Luminal B		LumB – Her2		Non-luminal		Triple negative	
	n	%	n	%	n	%	n	%	n	%
Upper-outer	210	49.3	73	44.0	18	43.9	7	53.9	40	57.1
Upper-inner	65	15.3	39	23.5	5	12.2	4	30.8	9	12.9
Lower-outer	47	11.0	20	12.1	4	9.8	0	0	9	12.9
Lower-inner	36	8.5	13	7.8	7	17.1	0	0	1	1.4
Central	62	14.6	17	10.2	7	17.1	2	15.4	6	8.6
Axillary process	6	1.4	4	2.4	0	0	0	0	5	7.1

Table 3
Correlation between the location of the primary breast tumour (column) and the subregional location of the SLN (row) if intratumoural injections were used (p = 0.016) and distribution pattern and metastatic status of the SLN in the subregions of the axilla.

	Upper outer	Lower outer	Upper inner	Lower inner	Central	Axillary process	Stained & removed SLN	Positive SLN	Positivity rate
anterior	65 (34.2%)	13 (41.9%)	28 (53.9%)	16 (69.6%)	12 (54.5%)	5 (45.5%)	349 (39.9%)	73	20.9%
central	55 (28.9%)	8 (25.8%)	15 (28.8%)	6 (26.1%)	5 (22.7%)	1 (9.1%)	245 (28.0%)	53	21.6%
posterior	60 (31.6%)	7 (22.6%)	6 (11.5%)	1 (4.3%)	2 (9.1%)	4 (36.3%)	203 (23.2%)	43	21.2%
lateral	6 (3.2%)	3 (9.7%)	3 (5.8%)	0 (0.0%)	1 (4.6%)	1 (9.1%)	48 (5.5%)	11	22.9%
apical	4 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.1%)	0 (0.0%)	30 (3.4%)	9	30.0%

Table 4
Coverage of axillary volumes by tangential fields (n = 61).

% (No.)		STgF	HTgF	p-value
Level I	Complete	0 (0)	65.6 (40)	<0.0001
	Partial	100.0 (61)	34.4 (21)	–
	Out of field	0 (0)	0 (0)	–
Level II	Complete	0 (0)	6.6 (4)	0.1198
	Partial	27.9 (17)	93.4 (57)	–
	Out of field	72.1 (44)	0 (0)	<0.0001
Level III	Complete	0 (0)	0 (0)	–
	Partial	8.2 (5)	90.2 (55)	–
	Out of field	91.8 (56)	9.8 (6)	<0.0001

STgF, standard tangential field; HTgF, high tangential field.

(rate of "out of field" with STgF or HTgF: 91.8% and 9.8%, p < 0.0001).

Discussion

The main objective of the study was to examine the presumable relationship between the quadrants of the breast and the subregions of the axilla and thus to describe a functional and morphologic lymphatic drainage pattern. Furthermore, the coverage of axillary volumes with tangential fields for WBI was also studied.

In summary, we did not find a significant correlation between the histopathological parameters of the primary breast cancer and the subregional location of the SLN. However, it is obvious from the data that the SLN is more than likely to be present in the anterior, posterior and central axillary subregions. Moreover, the SLN positivity rate in the lateral subregion (22.9%; n = 11) was not negligible. It is also clear from the data that upper-outer quadrant tumours spread least frequently to the anterior lymph nodes, while inner and central quadrant tumours have similar drainage patterns mainly to the anterior and central subregions.

There are several studies concerning the coverage of axillary lymph nodes from whole breast tangential field irradiation. Reed et al. [25] reported that using STgFs, no patient received complete coverage of the axillary Level I–II lymph node volume. They concluded that definitive irradiation of the Level I and II axillary lymph node regions required significant modification of the STgFs. Krasin et al. [26] showed that the use of STgFs does not therapeutically treat the regional lymph nodes. In their series, only 1 out of 25 patients had adequate coverage of the Level I region, and no patient had adequate coverage of Level II. Reznik et al. [27] observed that adequate coverage of Level I, defined when 95% of the volume received 95% of the dose, was achieved in none of the patients with normal tangents and in 6 patients (6 of 35) with high tangents. In a study by Orecchia et al. [28], the Level I nodes were only partially in the STgF, and the mean dose was only 48.7% of the prescribed dose. Our study was performed to address the issue of axillary volume coverage according to tangential field size. We showed that no patient had complete coverage of the Level I or Level II region with STgFs, and in 72.1% of the patients, the Level II volume was completely out of field. Using HTgF, 65.6% of the patients had complete coverage of Level I regions and the complete coverage rate was only 6.6% for Level II volume. The coverage of Level III region was very poor either with STgF (rate of out of field: 91.8%) or HTgF (rate of out of field: 9.8%).

Our results are consistent with the earlier studies that showed that STgF does not adequately cover the axillary volumes. With modern techniques, adequate coverage of the axillary volumes depends on the cranial field edge. Ohashi et al. [29] used 3D-CRT with a field-in-field technique, and half of the humeral head was inside the field. With this technique, even the dose to the Level III region was appropriate (V90 was 82.8%). In a study by Nagar et al. [30], when the tangential fields were modified to include Level I and II volumes, the mean dose (STgF vs. modified HTgF) increased from 35 Gy to 51 Gy and 11 Gy to 50 Gy, respectively. In patients studied by Belkacemi et al. [31], the STgF was defined with the cranial border set at 2 cm below the humeral head, while the HTgF consisted of a superior border placed at the inferior edge of the humeral head. The mean dose delivered to Level I with STgF or HTgF was 20 Gy and 33 Gy, respectively (p < 0.0001). We also used classical HTgF such as Belkacemi et al. [31], and the coverage of the Level I region was limited (complete coverage rate 65.6%). Attempts to increase the volume of complete coverage could induce a significant increase in lung dose. Alco et al. [32] suggested shaping the tangential field with multi-leaf collimators according to axillary level volumes to ensure complete coverage, but the inclusion of the axillary region in the target volume increased the irradiated lung volume. Mean lung dose was with the HTgF or multi-leaf collimators HTgF 6.5 and 9.6 Gy, respectively (p = 0.0001). To study the adequate coverage of the axilla, Levels I, II and III should be defined (delineated) by anatomical structures. STgFs provide limited coverage of the axilla, but HTgFs may provide complete coverage of Level I volume in some patients.

In our study, 9 (1.0%) positive SLNs were in the apical and 11 (1.3%) metastatic lymph nodes were in the lateral subregions. In total, 20 patients with positive lymph nodes (2.3% of our cases) would be left untreated if we applied tangential WBI to treat the axilla.

In our view, for the proper treatment of the axilla, an additional axillary and supraclavicular RT field is needed. This correlates with the findings of the Hungarian OTOASOR prospective randomised

clinical trial with axillary and supraclavicular field irradiation in the case of a metastatic SLN without ALND [33].

Applying the ARM technique, the lymph nodes stained with blue dye or radioisotope are preserved to prevent postoperative lymphedema. The subregional localisation of the ARM nodes has not yet been clearly identified, but it seems obvious that majority of the lymphatics draining the upper limb traverses deep in the axilla [17]. This was also confirmed by Ikeda et al. [34], who found ARM nodes in zones that correspond to mainly the lateral, apical and posterior axillary subregions.

In our study, 281 (32.1%) SLNs were found within one of these subregions, and 22.4% (n = 63) of them were positive. This means that 7.2% of all our cases had one positive lymph node in the expected ARM lymph node regions.

According to these results, due to the high rate of posterior subregional SLN drainage (21.8% n = 203) and SLN positivity (21.2%), not only the ALND but also the SLNB carry a high risk of a preserved positive lymph node and have a negative effect on the patient's successful treatment. This corresponds to the results that showed that the oncological safety of the ARM technique in patients with axillary lymph node metastasis from breast cancer is questionable [35,36], and proper indications, patient selection and further investigations are needed for the safe application of ARM [37].

Conclusion

Our findings suggest that there is no significant correlation between the histopathological parameters of the primary breast tumour and the subregional localisation of the SLN. The majority of SLNs are located in the anterior and central subregions.

When primary RT is used to treat the axilla, the contouring of the axillary lymph node levels is necessary for the proper design of the tangential field borders. Our analysis leads to the conclusion that STgF did not provide complete coverage of level I-II axillary lymph nodes. The use of high tangential fields is one means of improving axillary coverage with whole breast irradiation.

Tangential field WBI provides limited coverage of the axilla. Only 65.6% of our patients had complete Level I coverage with high tangential fields.

Moreover, using the ARM technique and leaving lymph nodes behind in the apical, lateral or posterior axillary subregions may leave behind up to 7.2% of metastatic lymph nodes, which may elevate the risk of possible understaging or undertreatment. In these cases, clipping the preserved lymph nodes is mandatory for adjuvant axillary RT.

Conflict of interest statement

All authors certify that there is no actual or potential conflict of interest in relation to this article.

Role of funding source statement

All authors certify that there were no funding sources; therefore, they did not play any role in data collection, analysis, interpretation, trial design, patient recruitment or any aspect pertinent to the study.

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