Radiotherapy and Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Location of arm draining lymph node in relation to breast cancer radiotherapy field and target volume

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ARTICLE INFO

Article history:
Received 11 September 2018
Received in revised form 26 October 2018
Accepted 28 October 2018
Available online xxxx

Keywords:
Breast cancer
Radiotherapy
Lymphoedema
ARM nodes
Sentinel nodes

ABSTRACT

Background: Lymphoedema of the arm following axillary surgery or radiotherapy remains a significant side effect affecting some women after breast cancer treatment. Axillary reverse mapping (ARM) is a technique used to identify the lymph node draining the arm (ARM node). Our study aim was to examine the location of the ARM nodes in relation to target volumes and treatment fields for breast cancer radiotherapy.

Materials and methods: Eighteen breast cancer patients underwent lymphoscintigraphy of contralateral arm (left 10, right 8) and SPECT CT scan on a research study. Patient position for the SPECT CT scan approximated the position used for radiotherapy. Using MIM software™, the ARM node for each subject was contoured on the SPECT CT and verified by a nuclear medicine physician. The CT component of the SPECT CT was then transferred to ECLIPSE™ radiotherapy planning software, and the contralateral breast and axilla were contoured on this CT scan according to the ESTRO contouring guideline. Two radiotherapy plans were generated for each subject using standard tangential IMRT technique at a dose of 50 Gy in 25 fractions, one treating contralateral breast alone, the other treating contralateral breast and contralateral axilla level 1–4. The ARM node was considered "within the radiotherapy field" if the mean dose received by the ARM node was more than 50% of the prescribed dose: i.e., 25 Gy.

Results: One right-sided subject had 2 ARM nodes, all others had 1 ARM node. All ARM nodes (left 10, right 9) were located within level 1 of the axilla. For the subject with 2 ARM nodes, the node that received a higher dose was used for the analysis. The mean dose received by the ARM node in the whole breast radiotherapy plans ranged from 0.8 to 45.5 Gy, with a median of 10.9 Gy. The mean dose received by the ARM node in the whole breast and axilla plans ranged from 43.4 to 52.5 Gy, with a median of 49.3 Gy. In the whole breast radiotherapy plans, only 5 out of 18 ARM nodes were found to be "within radiotherapy field", and only 2 ARM nodes received more than 40 Gy. In the breast and axilla plans, all 18 ARM nodes were "within radiotherapy field" and all received more than 40 Gy. To better visualise the locations of ARM nodes, all left sided ARM nodes were then mapped onto a CT set from one of the left-sided subjects, and all the right sided ARM nodes mapped onto one of the right-sided subjects, and digitally reconstructed radiograph (DRR) for radiotherapy fields were produced.

Conclusions: Our study demonstrates that the vast majority of ARM nodes (72%) are outside the tangential whole breast radiotherapy fields. In our study, all the ARM nodes were within the axillary radiotherapy fields covering level 1–4 axillary volumes according to the ESTRO contouring guideline, and complete shielding of the humeral head according to the EORTC consensus did not lead to sparing of the ARM nodes. A prospective study is needed to examine the oncological safety of ARM node-sparing axillary radiotherapy and its potential to reduce the risk of arm lymphoedema.

Lymphoedema of the ipsilateral arm following axillary surgery or radiotherapy remains a risk affecting some women after breast cancer treatment. Axillary reverse mapping (ARM) is a technique used to identify the lymph nodes and lymphatic channels draining the upper limb (ARM node) with the aim of preserving these during axillary surgery in breast cancer patients to prevent lymphoedema. A previous study from our institution [1] investigated the prevalence and predictors of ARM node involvement with

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https://doi.org/10.1016/j.radonc.2018.10.038
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breast cancer metastases in patients undergoing an axillary lymph node dissection (ALND). About one quarter of patients with positive axillary nodes had ARM node involvement; however, it may be safe to preserve the ARM node for some women.

Results from randomized controlled trials (ACOSOG Z0011 [2] and AMAROS [3]) have led to the avoidance of ALND for some women with positive sentinel nodes, replacing it with either no further axillary treatment as in the ACOSOG Z0011 trial in women who had whole breast radiotherapy, or axillary radiotherapy as in the AMAROS trial. The AMAROS trial showed that axillary radiotherapy provides excellent and comparable axillary control compared to completion ALND after positive sentinel node biopsy, with significantly less risk of lymphoedema. Clinically significant lymphoedema defined as arm circumference increase $\geq$10% occurred in 6% of patients who underwent axillary radiotherapy, compared to 13% of patients who underwent ALND. The irradiation of the ARM node could have contributed to the risk of lymphoedema for patients undergoing axillary radiotherapy. Furthermore, breast radiotherapy alone frequently leads to incidental irradiation of the lower axilla and it is not clear whether the ARM nodes are receiving significant radiation dose during this treatment.

Our study aims to examine the location of the ARM nodes in relation to standard target volumes and treatment fields for radiation treatment to the breast and axilla and analyse the dose received by the ARM nodes.

Materials and methods

Eighteen women with breast cancer underwent lymphoscintigraphy of the contralateral arm and SPECT CT scan on a research study. Their baseline characteristics are shown in Table 1 (supplementary material). The research protocol was approved by the Western Sydney Local Health District Human Research Ethics Committee (WSLHD-HREC). Prior to enrolment, all participating patients signed WSLHD-HREC approved consent forms.

In addition to receiving peri-tumoral injections of ^{99m}Tc-sulphur colloid for pre-operative sentinel node localisation for the ipsilateral breast cancer, all patients received an additional intradermal injection of ^{99m}Tc-sulfur colloid in the 2nd dorsal inter-digital web space of the contralateral hand. In total, 10 patients had injections into their left hand and 8 patients had injections into their right hand.

Patient position for the SPECT CT scan approximated the position used for radiation treatment; their arms were abducted to 150–160° and externally rotated to 90°. Using MIM software™ (v6.4; MIM Software Inc., Cleveland, OH) which fuses SPECT and CT, the ARM node for each subject was contoured on the SPECT CT. The volume of this ARM node was approximately a 1 cm sphere (Fig. 1). The position of the ARM node was verified by a nuclear medicine physician. The CT component of the SPECT CT was then transferred to ECLIPSE™ radiotherapy planning software (v13.7; Varian Medical Systems, Palo Alto, CA), and contralateral breast

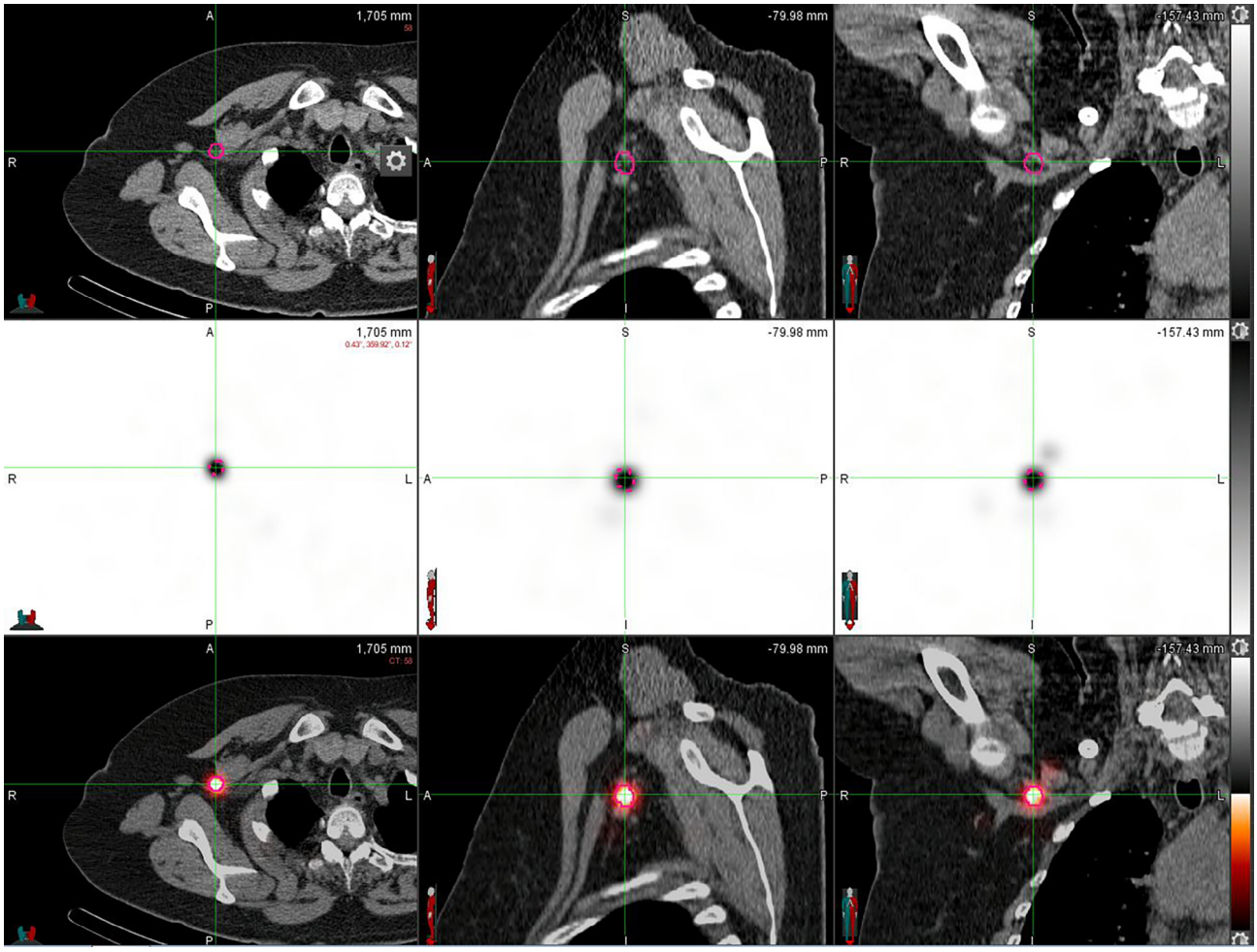

Fig. 1. The ARM node for each patient was contoured on the SPECT CT using MIM software™.

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and axilla volumes on the side of the ARM node were contoured by a radiation oncologist according to the ESTRO contouring consensus guideline [4].

Two radiotherapy plans were generated for each subject using standard tangential IMRT technique at a dose of 50 Gy in 25 fractions. One plan was created for radiotherapy treating the contralateral breast alone (Fig. 2), the other plan for treating contralateral breast and contralateral axillary lymph nodes (Fig. 3). In the tangential IMRT plans treating breast alone, typically 60% of the dose was delivered with forward-planned conventional tangential fields (6 MV photons), and 40% of the dose was delivered using inverse-planned IMRT (6 MV photons). At least 95% of breast PTV was covered by 95% of prescribed dose (47.5 Gy). In the radiation therapy plan treating breast and axilla, a hybrid 3D-conformal radiotherapy and tangential IMRT technique was used. The supraclavicular and high axillary nodes were treated with two to four modified AP/PA fields, angled to avoid midline structures such as spinal cord, trachea and oesophagus. The junction between the supraclavicular and tangential IMRT plan was placed at the inferior aspect of the head of the clavicle.

The mean dose received by the ARM node was calculated in each plan, and the ARM node was considered "within the radiotherapy field" if the mean dose received was >50% of the prescribed dose, i.e., >25 Gy.

Results

One right-sided patient had two ARM nodes, all other patients had only one ARM node identified. All ARM nodes were found

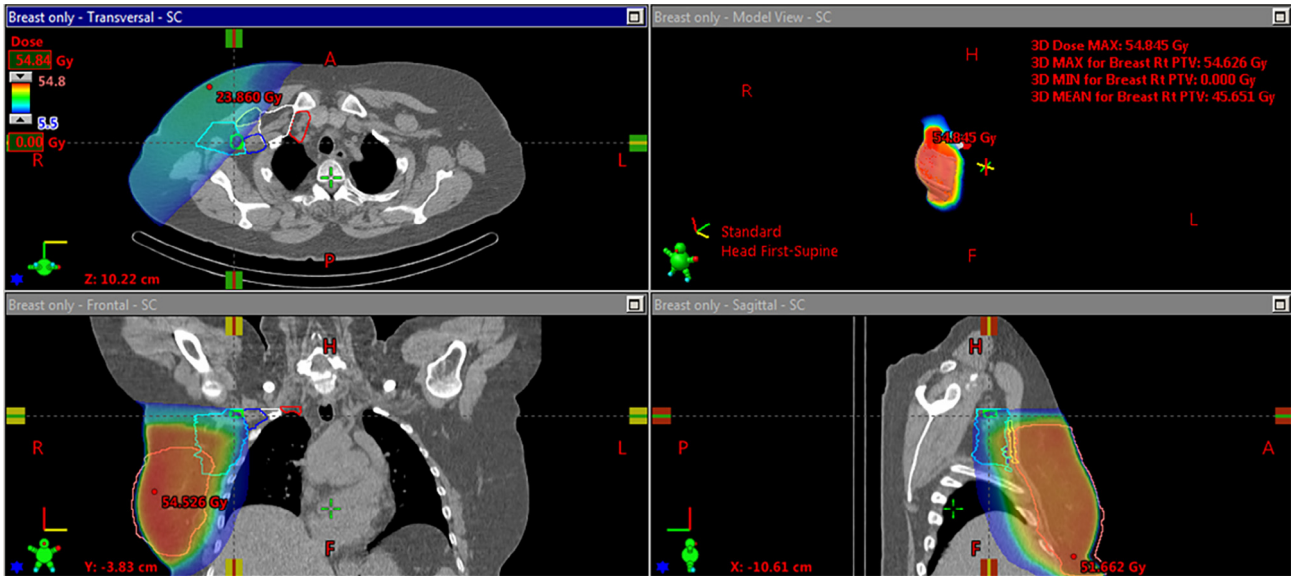

Fig. 2. Radiation therapy plan treating breast alone. ARM node in green, level 1 axilla in cyan, level 2 axilla in blue, interpectoral space in yellow, level 3 axilla in white, level 4 axilla or lower supraclavicular fossa in red, breast PTV in pink. ARM, axillary reverse mapping; PTV, planning target volume. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

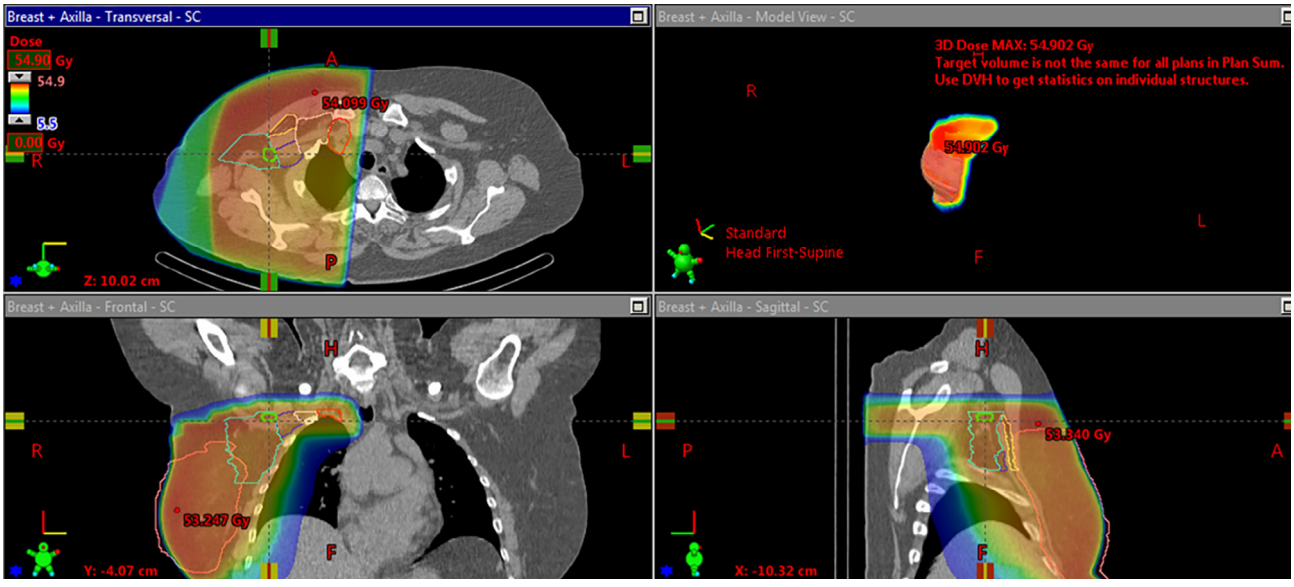

Fig. 3. Radiation therapy plan treating breast and axilla. ARM node in green, level 1 axilla in cyan, level 2 axilla in blue, interpectoral space in yellow, level 3 axilla in white, level 4 axilla or lower supraclavicular fossa in red, breast PTV in pink. ARM, axillary reverse mapping; PTV, planning target volume. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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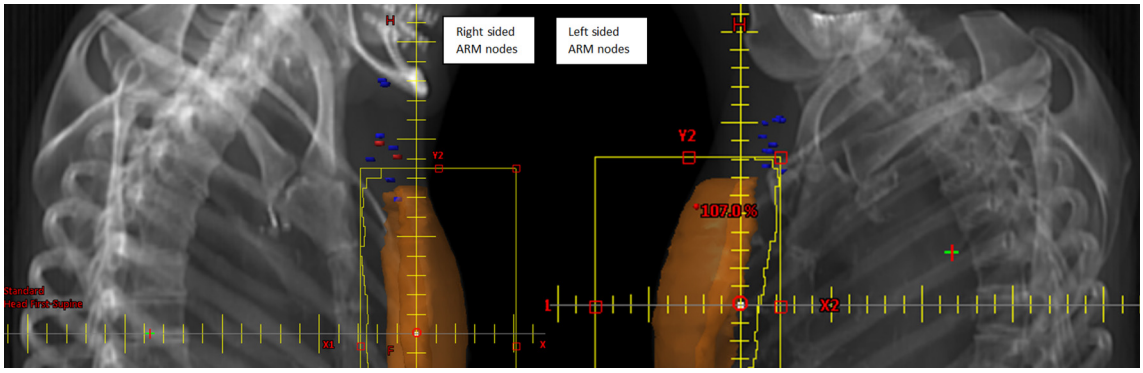

Fig. 4. DRRs of the right and left lateral tangential fields in the whole breast radiotherapy plans. The ARM nodes are shown in blue, the two ARM nodes belonging to the same patient are shown in red. DRR, digitally reconstructed radiograph; ARM, axillary reverse mapping.

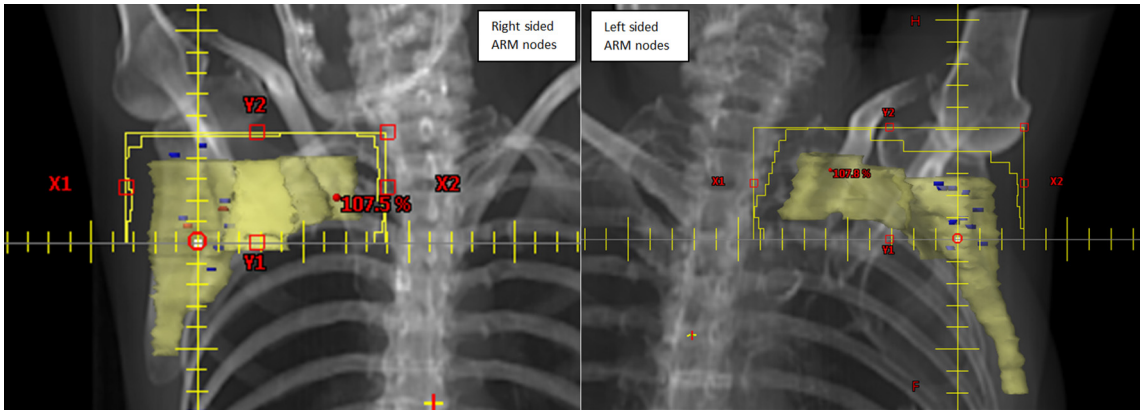

Fig. 5. DRRs of the right and left anterior oblique axillary fields in the breast and axilla radiotherapy plans. The ARM nodes are shown in blue, the two ARM nodes belonging to the same patient are shown in red. DRR, digitally reconstructed radiograph; ARM, axillary reverse mapping. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

within level 1 of the axilla. For the patient with two ARM nodes, the node that received a higher dose was used for the analysis.

The mean dose received by the ARM node in the whole breast radiotherapy plans ranged from 0.8 - 45.5 Gy, with a median of 10.9 Gy. In the whole breast radiotherapy plans, only 5 out of 18 ARM nodes received more than 25 Gy, and were therefore considered to be "within the radiotherapy field". Only 2 of 18 ARM nodes received more than 40 Gy.

The mean dose received by the ARM node in the whole breast and axilla plans ranged from 43.4 to 52.5 Gy, with a median of 49.3 Gy. In the breast and axilla plans, all 18 ARM nodes were "within the radiotherapy field", and in fact all received more than 40 Gy.

To better visualise the location of ARM nodes, all left-sided ARM nodes were transferred onto a single CT data set from one of the left-sided patient according to bony and soft-tissue anatomy, and all the right sided ARM nodes were transferred onto a single CT data set from a right-sided patient. Digitally reconstructed radiographs (DRR) for radiotherapy fields were then produced for the template left-sided and right-sided patients. The DRR of the lateral tangential field in the whole breast radiotherapy plan is shown in Fig. 4, and the DRR of the anterior oblique axillary field in the breast and axilla radiotherapy plan is shown in Fig. 5.

Discussion

A previous study of lymphatic channels of upper limbs based on careful cadaver dissection showed that most lymphatic vessels were seen to flow into one main sentry lymph node in the axillary region [5]. This lymph node can be identified by an ARM technique, and damage to the ARM node and its immediate surrounding lymphatic vessels by surgery or radiotherapy can potentially increase the risk of treatment-induced lymphoedema of the upper limb.

In our study, we found that the ARM nodes of all 18 patients were within level I of the axilla. This is different from a previous study by Cheville et al. [6] that showed 62.5% of ARM nodes with the highest radioactivity count were located in levels I and II of the axilla, 15.6% were located in level III and 21.9% were located in the supraclavicular fossa. However, in the study by Cheville et al. lymphoscintigraphy of the arm and SPECT CT were performed after the patients' axillary procedures; 16 patients in their study had sentinel node biopsy and another 16 patients had axillary clearance. The disruption of the lymphatics by surgical procedures may have led to inaccuracy in the identification of the ARM nodes, especially since the ARM node is usually included in a complete ALND. On the contrary, in our study none of the patients had any surgical treatment to the axilla prior to the lymphoscintigraphy and SPECT CT scan. Among the 16 patients in the study by Cheville et al. who had the more limited axillary procedure of sentinel node biopsy, the majority of the ARM nodes (81.3%) were detected in levels I and II of the axilla.

The ARM node and sentinel node(s) draining the breast are distinctly separate lymph nodes in the vast majority of cases. A systemic review by Ahmed et al. [7] showed a crossover rate of up to 10%, and the previous study from our institution by Ngui et al. [1] also confirmed low crossover rate of 9.6%. In our study, we

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demonstrated that most of the ARM nodes (13 out of 18, 72%) were located in the upper level 1 axilla, outside the tangential whole breast radiotherapy fields. On the contrary, a study by Rabinovitch et al. [8] showed that the majority (78%) of sentinel nodes of the breast were located in the lower axilla within the tangential breast radiotherapy fields, indicating the breast and arm drain to different primary nodes. In our institution, breast surgeons routinely leave a clip at the site of the breast sentinel node biopsy, and in a review of 20 consecutive cases of patients undergoing tangential radiotherapy to the breast alone, axillary SLN clips were found within the breast radiotherapy fields in 16 cases (unpublished data), consistent with the finding by Rabinovitch et al.

Our study also showed that the ARM nodes were well within the axillary radiotherapy fields, with all ARM nodes receiving 40 Gy or more. The contouring and planning of the axillary radiotherapy was carried out according to the EORTC consensus guideline, and complete shielding of the humeral head according to the EORTC consensus did not lead to sparing of the ARM nodes.

In the study by Ngui et al. [1], patients received blue dye injection in the upper arm for ARM node localisation, all patients had an axillary clearance with the identified ARM node sent separately for histologic analysis, and metastatic involvement of the ARM node was found in 27% of cases. However, a significant proportion of the patients in that study had clinically involved axillary lymph nodes at diagnosis. When the analysis was restricted to patients with clinically negative axillary nodes who then had axillary clearance after a positive breast sentinel node biopsy, only 1 out of 16 (6.3%) patients had metastatic involvement of the ARM node. These results suggest that sparing of the ARM node is potentially safe when restricted to patients with clinically negative axillary lymph nodes who were then found to have a pathologically positive sentinel node.

There are ongoing controversies regarding the management of the clinically negative axilla after a positive sentinel node biopsy. A study by Jagsi et al. [9] examined radiation field design in the ACOZOG Z0011 trial and showed that high tangent radiation therapy fields were used in 52.6% of patients in the sentinel node-only arm of the study and 18.9% received regional nodal radiotherapy with at least three radiation fields. This finding indicates that significant radiation therapy coverage of the axilla occurred among patients in the sentinel node biopsy-only arm of the Z0011 trial. An alternative approach is to recommend full axillary radiotherapy after a positive sentinel node biopsy, as supported by the AMAROS study [3], but this approach can be associated with clinically significant lymphoedema of the upper limb in at least 6% of the patients. The pilot study by Cheville et al. [6], showed that radiation therapy can be delivered to the axilla while sparing the ARM node using an intensity modulated radiation therapy technique. An individualised treatment approach can be undertaken, where the ARM node for each patient is identified during radiotherapy planning, and intensity modulated radiation therapy technique as described by Cheville et al. can then be used to treat the axilla while avoiding high dose radiation to the ARM node. ARM node-sparing axillary radiotherapy, if validated by a prospective clinical trial, may represent another management approach for selected patients, a compromise between observation alone and full axillary radiotherapy.

There are potential limitations of our study. First of all, the study by Suami et al. [5] showed that some lymph vessels running along the posterior forearm may bypass the ARM node to reach other smaller nodes, so perhaps adding a second injection site in the anterior forearm or cubital fossa may improve the accuracy of detecting the main sentinel node draining the arm. Secondly, patients' arm positions used in the SPECT CT scan were slightly more abducted when compared to those used in the radiation treatment, which may impact the dose received by the ARM nodes by breast/axillary radiation treatment.

In conclusion, our study demonstrated that nearly three quarters of the ARM nodes (72%) were located outside the standard tangential whole breast radiotherapy fields and received relatively low dose. On the other hand, all the ARM nodes were well within the standard axillary radiotherapy fields. The radiation dose received by the ARM node during breast cancer radiation treatment may contribute to the risk of development of arm lymphoedema. A prospective study is needed to examine the oncological safety of ARM node-sparing axillary radiotherapy and its potential to reduce the risk of arm lymphoedema.

Conflicts of interest

No conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.10.038.

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