An Update on Regional Nodal Irradiation: Indication, Target Volume Delineation, and Radiotherapy Techniques

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Keywords

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Abstract

Background: Tremendous changes have occurred in the treatment of breast cancer. This paper reviews and unifies the available data on modern axillary management of breast cancer patients with focus on the target volume delineation for regional nodal irradiation according to the most important contouring guidelines, the European Society for Radiotherapy and Oncology (ESTRO) and the Radiation Therapy and Oncology Group (RTOG). **Summary:** The use of extensive radiotherapy target volumes (level I, II, III, IV) is probably not necessary for all patients to reproduce the clinical benefit shown in the available randomized trials (EORTC, MA.20, AMAROS, Z0011). Nevertheless, given the results in the MA.20 trial, where the patients received more modern systemic therapies and high irradiation doses in the medial paraclavicular region (level IV) and level II, it can be justified to include these regions completely in selected high-risk patients. **Key Messages:** High-tangent irradiation results in a similar dose distribution in axillary levels I and II compared to the AMAROS treatment field design in some patients. This supports earlier assumptions that irradiation may have accounted for the good results after sentinel lymph node dissection alone in the Z0011 trial. The ESTRO and RTOG clinical target volume (CTV) definitions cover sufficiently the metastatic lymph node hotspots, with a better coverage for the ESTRO CTV. Further, contouring according to the ESTRO would spare a significantly larger part

of the healthy lymphatic system, making it our preferred contouring atlas. Modern radiotherapy techniques, such as deep inspiration breath hold, should be cautiously employed in patients treated according to the inclusion criteria of the Z0011 as it will result in a lower dose to the axillary levels.

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Introduction

Axillary lymph node dissection (ALND) has a long tradition in breast cancer therapy and was reported as early as 1907 by Halsted [1]. ALND usually implies the removal of ≥ 10 lymph nodes – located mainly in level I and level II – and has the advantage of reliably identifying nodal metastases. Nonetheless, it is associated with significant morbidity [2]. Further, the impact of ALND on survival has long been disputed. The 25-year findings of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial failed to show a significant survival advantage from removing occult positive nodes at the time of initial surgery [3], but meta-analyses demonstrated a benefit [4]. Thus, ALND remained a long-time standard for positive lymph nodes [5]. This changed with the publication of the Z0011 trial, where no differences were found between ALND and no-ALND after positive sentinel nodes. On the other hand, regional node irradiation is a crucial part of the adjuvant therapy in patients with lymph node-positive early breast cancer.

Data from the MA.20 [6] and EORTC 22922-10925 (EORTC) trials [7] have proven that the addition of the

Fig. 1. RTOG and ESTRO contouring recommendations.

supraclavicular and internal mammary lymph node region is effective in improving regional and distant control as well as disease-specific mortality compared to whole-breast or chest-wall irradiation alone.

Furthermore, results from the EORTC 10981-22023 AMAROS trial (AMAROS) revealed that axillary radiotherapy to levels I, II, and III after positive sentinel node biopsy provides excellent axillary control for patients with T1–2 primary breast cancer even when ALND is omitted [8].

In the last decades, tremendous changes occurred in radiation oncology with several new irradiation techniques being employed and routinely used for breast cancer patients. However, with the establishment of computed tomography (CT)-based treatment planning and precise irradiation techniques, definition of the nodal target volume has nowadays become the “weakest part of the quality chain in lymph node radiotherapy” [9]. In order to minimize these uncertainties, contouring atlases were published in 2009 by the Radiation Therapy and Oncology Group (RTOG) (<https://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx>) and in 2015 by the European Society for Radiotherapy and Oncology (ESTRO). Unfortunately, the atlases differ significantly from each other (Fig. 1).

This paper aims to review the available data on modern axillary management of breast cancer patients with focus on the target volume delineation for regional nodal irradiation according to the most important contouring guidelines, ESTRO and RTOG.

Changes in the Surgical Management of the Axilla

Sentinel lymph node dissection (SLND) is a minimally invasive procedure for the detection of occult lymph node metastases [10]. The Z0011 trial randomized between SLND and SLND followed by ALND in SLN-positive patients with clinically negative lymph nodes [11]. The study targeted an enrollment of 1,900 women with

final analysis after 500 deaths, but the trial closed early because the mortality rate was lower than expected. However, the study changed the treatment approach for SLN-positive patients with clinically negative lymph nodes. Among patients with limited SLN affected, treated with breast conservation and systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival. Thus, patients – if they are within the inclusion criteria of Z0011 – nowadays receive only SLND. Nonetheless, even if the Z0011 protocol required that patients “receive whole breast RT using standard tangential fields without a third field directed to the lymph node areas” a significant proportion of the patients were not irradiated according to the recommendation [12]: half of the analyzed patients had high tangents and approximately 19% received directed regional nodal irradiation with more than three fields. Most high tangents in the radiotherapy treatment plans covered part of levels I and II of the axilla and thus underlined the importance of radiotherapy to locoregional lymphatics.

Understanding the Radiotherapy Techniques and the Dosimetry of Randomized Trials on Locoregional Lymphatic Irradiation

All the previously cited radiation oncology studies were launched in the 1990s and early 2000s with very basic radiotherapy techniques (mostly 2D radiotherapy). The study treatment arms, radiotherapy beam arrangements, and prescribed dose were as follows:

AMAROS

Patients were randomly assigned to receive either ALND or axillary radiotherapy in the case of a positive sentinel node. ALND and axillary radiotherapy both resulted in excellent and comparable axillary control for patients with T1–2 primary breast cancer and no palpable lymphadenopathy. Axillary radiotherapy resulted in significantly less morbidity.

All three levels of the axilla with the medial part of the supraclavicular fossa were considered as target areas for radiotherapy [8].

The coracoid process was used as a radiological landmark. Treatment of full patient thickness was necessary for levels I and II (lateral to the coracoid process). The target volume of level III could be defined at a depth of 3 cm from the anterior skin surface. The cranial border was determined by the sternoclavicular joint (which was included with a margin of 3 cm), the medial border by the midline of the sternum, and the lateral border by the insertion of the major pectoral muscle at the humerus. The caudal border could be the cranial end of the chest wall or breast fields but had to be at least at the level of the sternal insertion of the second rib (angulus sterni) medially and at the level of the fourth rib laterally.

An anterior photon field was given with the above-mentioned field borders; a smaller posterior-anterior photon field was given with identical field borders except for the medial border, which is situated at the coracoid process. The prescribed dose to the axilla as a whole was 50 Gy in 25 fractions of 2 Gy.

EORTC

Women who had a centrally or medially located primary tumor irrespective of axillary involvement and women with an externally located tumor with axillary involvement were included. Patients were randomly assigned to either whole-breast/thoracic-wall radiotherapy and regional nodal irradiation (nodal-irradiation group) or whole-breast/thoracic-wall irradiation alone (control group). Disease-free survival and distant disease-free survival were improved by irradiation of the nodal basin and the breast cancer mortality was reduced.

The target volumes of the group with regional nodal irradiation included the medial supraclavicular and the internal mammary lymphatics [7]. The lateral border was at the middle of the clavicle and the upper border was 3 cm above the head of the clavicle. The medial border was 1 cm across the midline but also had to be defined clinically at the supraclavicular region by the patient's radiation oncologist. The lateral field border of the internal mammary part of the field lay 5 cm lateral from the midline. The lower field border was defined by the lower border of the fourth rib. The lymph node irradiation fields were matched to the tangential fields of the breast.

Anterior-posterior fields were used for the coverage of the lymphatics with a combination of photons and electrons (mixed beam). The prescription point for photons was defined at a depth of 3 cm on the beam axis. For electrons, the dose was specified at the prescription point, which was defined as the depth of the maximal dose. Doses were applied up to 26 Gy with photons (max. 10 MV) and up to 24 Gy with electrons (12–14 MeV) with 2 Gy per fraction. Thus, the prescribed dose in the target volume was 50 Gy in 2-Gy fractions.

MA.20

Women with node-positive or high-risk node-negative breast cancer who were treated with breast-conserving surgery and adjuvant systemic therapy were randomized to either whole-breast irradiation plus regional nodal irradiation (including internal mammary, supraclavicular, and axillary lymph nodes) (nodal-irradiation group) or whole-breast irradiation alone (control group). Similar to the EORTC trial, the addition of regional nodal irradiation to whole-breast irradiation did not improve overall survival but reduced the rate of breast cancer recurrence and improved disease-free survival.

The upper internal mammary, supraclavicular, and axillary region (level I–III) nodes were included in the lymphatic treatment field [6]. For this, a 4-field and a modified wide tangent technique (50 Gy/2 Gy) were used to cover the internal mammary nodes as well as the mammary gland. The breast, internal mammary nodes, and lower axilla were treated with modified wide tangents. The medial border corresponded to a line 3 cm contralateral to the mid sternum to include the ipsilateral internal mammary nodes as well as the breast. For planning purposes, the lower border of the anterior third intercostal interspace and the lower half of the circumference of the breast was marked with wire. A cardiac and/or lung shield was placed in the inferior, posterior part of the field. Placing of this shield was guided by the outline of the breast and the location of the third intercostal interspace. Below the third interspace the blocking was placed for the medial tangent at the mid sternum. The amount of lung tissue in the upper half of the field had to be >2 cm and ideally <3.5 cm. In the lower half of the field, the amount of lung tissue had to be <2 cm to avoid excessive cardiac or lung radiation. The supraclavicular and axillary regions were treated with an anterior field with a prescribed dose at 3 cm of 50 Gy (scenario I). An additional posterior field to the axilla was used in all patients with <10 nodes removed or >3 positive nodes (scenario II). For this scenario the dose was prescribed mid axillary and was 45 Gy with 1.8 Gy per fraction.

Z0011

ACOSOG Z0011 randomized women with clinical T1–2 invasive breast cancer, no palpable adenopathy, and 1–2 SLNs containing metastases to undergo ALND after SLND or no further axillary-specific treatment. Among patients with limited SLN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival.

As previously described, a considerable proportion of the patients, however, received high tangents (defined by cranial tangent border ≤ 2 cm from the humeral head) [11]. The planning target volume prescribed dose was 50 Gy with 2 Gy per fraction.

In order to treat modern patients, we need to translate all this surgical and radiotherapeutic information into contemporary approaches. Thus, several topics should be revisited and reanalyzed.

Translating Surgical Information into Imaging

SLNs are mainly located in levels I and II [10]. In patients receiving SLN the drainage of the breast is towards the axilla (levels I and II), the internal mammary chain, interpectoral area, medial and lateral intramammary re-

Fig. 2. 3D atlas of location of healthy lymph nodes.

gion, and subclavicular and supraclavicular regions [13]. Nonetheless, in almost 70% of the cases, SLNs are negative and thus patients would not require an SLND at all [14]. As most patients undergo staging imaging beforehand, reliable information on metastatic lymph nodes would be imperative. However, the surgical/pathological information cannot yet be replaced by imaging information.

We focused on the localization of healthy as well as of pathological lymph nodes in CT and PET-CT imaging. According to our studies, most lymph node metastases occurred in level I dorsolateral to the musculus pectoralis minor and 1–3 cm below the subclavian vein. Lymph node metastases in levels II, III, and IV accumulated in close proximity to the subclavian vein [15].

“3D lymph node atlases” were created in order to illustrate the physiological and the pathological lymphatic drainage system (Fig. 2, 3) [15, 16]. Distributions of metastatic and healthy lymph nodes were found to be

clearly different within the lymphatic system. Often metastatic lymph nodes occurred outside the regions where healthy lymph nodes were detected by imaging. For example, in levels II and III the overlap between healthy and pathological lymph nodes was outstandingly small [15–17].

Translating Radiotherapy Data of Randomized Trials into 3D Treatment Planning Data

As previously described, available randomized trials relied mostly on 2D information. To recreate the 2D field design on modern CT data sets was imperative [18]. Due to the “simple” dose prescriptions at a specific depth and different techniques used in the randomized studies, significant differences between the studies and between different body shapes (slender patients, obese patients) was found in the coverage of the lymphatics.

Fig. 3. 3D atlas of pathological lymph nodes.

Axillary Levels I and II

Treatment of axillary levels I and II was intended in the AMAROS and the MA.20 trial. Most patients in the AMAROS trial would have received the prescribed 50 Gy. As expected, the MA.20 treatment plan without an additional “axilla posterior field” (scenario I) would have led to lower doses in the axillary lymph nodes compared to scenario II (level I: 35.1 ± 15.8 Gy vs. 49.9 ± 4.5 Gy). However, the doses would also have been dependent on the body shape of the patients. Obese patients would have had a lower dose than the prescribed 45 Gy in the MA.20 trial (level I: 36.3 ± 15.2 Gy). Neither the Z0011 nor the EORTC treatment plans purposely included axillary levels I and II in the target volumes. Correspondingly, the doses for the patients treated in these trials would have been lower compared to the AMAROS and MA.20. Both the Z0011 and the EORTC would – due to the techniques used – have applied an unintended radiotherapy dose to the axilla. The extent of incidental irradiation to the axil-

lary nodes would have been highly dependent on the patient’s body shape with the lowest values for a slender patient with small breasts [18].

Paraclavicular Lymphatics

The EORTC, MA.20, and AMAROS trials included the medial supraclavicular fossa in the target volume. However, the dose in the supra-/infraclavicular region would have again varied depending on treatment plan design and patient body shape. We could demonstrate that the best dose coverage would have been for the MA.20 field technique for the slender patient. The EORTC treatment field design led to significantly lower doses compared to the MA.20 field design in the supra-/infraclavicular region. Treatment of the supra-/infraclavicular region was not intended in the Z0011. Correspondingly, dose distribution in the supraclavicular region was negligible in all patients treated similarly to the Z0011 (<5.0 Gy). However, relevant incidental irradiation was ob-

Table 1. Healthy lymph node localization within the ESTRO guideline

Lymph node region	ESTRO guideline					
	inside		partly inside		outside	
	absolute, <i>n</i>	relative, %	absolute, <i>n</i>	relative, %	absolute, <i>n</i>	relative, %
Level I	521	38.8	463	34.5	358	26.7
Level II	115	56.4	72	35.3	17	8.3
Level III	8	40.0	10	50.0	2	10.0
Level IV/supraclavicular	27	9.4	50	17.4	210	73.2
Internal mammary	6	11.5	8	15.4	38	73.1
Intraglandular	1	2.9	0	0.0	33	97.1
Total	678	35.0	603	31.1	658	33.9

Table 2. Healthy lymph node localization within the RTOG guideline

Lymph node region	RTOG guideline					
	inside		partly inside		outside	
	absolute, <i>n</i>	relative, %	absolute, <i>n</i>	relative, %	absolute, <i>n</i>	relative, %
Level I	737	54.9	383	28.5	222	16.5
Level II	60	29.4	71	34.8	73	35.8
Level III	3	15.0	8	40.0	9	45.0
Level IV/supraclavicular	123	42.9	86	30.0	78	27.2
Internal mammary	7	13.5	10	19.2	35	67.3
Intraglandular	1	2.9	0	0.0	33	97.1
Total	931	48.0	558	28.8	450	23.2

served for the high-tangent treatment plans in the infraclavicular region with doses ranging between 30.0 ± 19.8 and 35.3 ± 19.4 Gy [18].

Internal Mammary Region

The MA.20 and the EORTC treatment arms included irradiation of the internal mammary lymph node region. Accordingly, the lymph nodes were covered by the prescribed doses. A standard tangential field arrangement as performed nowadays in breast cancer would, however, also cover the internal mammary lymph node region with a relevant dose, for example, the MA.20 dose would be 42.5 ± 14.8 Gy, the EORTC dose would be 39.3 ± 11.1 Gy, and the 3D-CRT tangential dose would be 30 ± 17.1 Gy. As before, the anatomy of the patient would also be important: an obese patient would have received a lower dose to the internal mammary compared to a slender patient. The Z0011 and AMAROS treatment plans both led to incidental irradiation of the internal mammary region, with only small differences between standard 3D-CRT tangential and high tangents, but significantly higher doses in the AMAROS treatment plan [18].

Comparison of Available Contouring Guidelines to the Actual Localization of Lymph Nodes

As previously described, the ESTRO and the RTOG both provided contouring guidelines for breast cancer (Fig. 1). The differences between the two guidelines are mostly related to the cranial, caudal, and dorsal border of the axillary and supraclavicular levels. Further, the ESTRO guideline – as it based its recommendation on conventional simulator-based radiotherapy – resulted in smaller target volumes. The ESTRO committee pointed to the fact that previous guidelines – including the RTOG guidelines – result in larger treated volumes compared to techniques being employed and routinely used by radiation oncologists.

Some studies are available on the appropriateness and pertinence of the two atlases [19–21]. For example, Gentile et al. [19] analyzed 30 breast cancer patients and found approximately 80% of lymph nodes to be partly outside the cranial and anterior borders of level I as delineated according to the RTOG. Chang et al. [21], on the other hand, used a “representative” CT in which they manually matched lymph nodes as 5-mm spots. Overall, the RTOG CTV failed to include the location of lymph node metastasis in 17.5% and the ESTRO CTV in 31.5%. DeSelm et

al. [20] performed a similar study with manual mapping of lymph nodes as 5-mm circles. All these studies, however, did not comprehensively take the shapes and sizes of the lymph nodes into account.

In the study performed by our group on PET-CT datasets, the occurrence of lymph node metastases inside the RTOG and ESTRO margins in patients was similar to that in the available literature. Further, both atlases performed similarly with regard to the coverage of lymph nodes. The largest geometric deviations between RTOG/ESTRO CTV contours and lymph node occurrence were measured in the supraclavicular and internal mammary regions [15]. Both the RTOG and the ESTRO CTV sufficiently cover the detected “hot spots” within the lymphatic drainage system, with a better coverage of the hotspots for the ESTRO CTV [15]. Nonetheless, regarding the internal mammary region, a larger proportion of the lymph nodes occurred outside the defined internal mammary CTV in our study compared, for example, to that of Chang et al. [21]. This can be explained by the fact that the lymph nodes in our study were represented in their actual size rather than as a 5-mm spot representing the epicenter.

Nevertheless, an incomplete coverage of lymph nodes does not automatically imply the necessity for larger CTVs in the future. An extension of CTVs must be discussed carefully, as minor changes in the target volume may result in drastic changes of the dose in the organs at risk. Such an organ at risk is the healthy lymphatic system in breast cancer radiotherapy.

The ESTRO CTV does not include a large proportion of healthy lymph nodes: many lymph nodes are either partially outside or outside the CTV (approx. 60%) [16]. Thus, a large part of the physiological lymphatic flow will not be irradiated if lymphatics are targeted by radiotherapy planned according to the ESTRO CTV (Table 1).

The RTOG encompassed a significantly higher proportion of healthy lymph nodes: 48% of healthy lymph nodes were completely within and 28.8% were partly within/outside (Table 2) [22].

Radiotherapy Techniques and Their Implication for Breast Cancer

Due to the deep inspiration anatomical changes that occur (e.g., an anterior/superior movement of the mammary gland) [23], the aim of our study was to evaluate the movements and doses of lymph node levels I, II, and III for irradiation in free breathing and deep inspiration breath hold (DIBH) and thus to understand the differences in the “accidental” regional nodal irradiation. We found a significant dose reduction due to DIBH in level I [24]. Similar results were reported in irradiation of the breast and lymphatics [25].

Conclusion

In summary, the use of extensive target volumes is probably not necessary for all patients to reproduce the clinical benefit shown in the available randomized trials. Nevertheless, given the high doses in most of the paraclavicular and level II lymph nodes in the MA.20 trial, inclusion of axillary level II in target volumes and extension of the supraclavicular CTV can be justified in selected high-risk patients.

High-tangent irradiation resulted in a similar dose distribution in axillary levels I and II compared to the AMAROS treatment field design in some patients. This supports earlier assumptions that irradiation may have accounted for the good results after SLND alone in the Z0011 trial.

The ESTRO and RTOG CTV definitions sufficiently cover the metastatic lymph node hotspots, with a better coverage for the ESTRO CTV. Further, contouring according to the ESTRO would spare a significant larger part of the healthy lymphatic system, making it our preferred contouring atlas.

Modern radiotherapy techniques, such as DIBH, should be cautiously employed in patients treated according to the inclusion criteria of the Z0011 as it will result in a lower dose to the axillary levels.

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