



Guidelines

Vessel based delineation guidelines for the elective lymph node regions in breast cancer radiation therapy – PROCAB guidelines



Karolien Verhoeven^{a,*}, Caroline Weltens^a, Vincent Remouchamps^b, Khalil Mahjoubi^b, Liv Veldeman^c, Benoit Lengele^d, Eszter Hortobagyi^a, Carine Kirkove^d

^a University Hospitals Leuven/KU Leuven; ^b Clinique Sainte Elisabeth (AMPR), Namur; ^c Ghent University Hospital; and ^d Catholic University of Louvain, Brussels, Belgium

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ABSTRACT

Objective: A national project to improve the quality of breast radiation therapy was started, named PROCAB (PROject on CAncer of the Breast). One of the objectives was to reach a national consensus guideline for the delineation of the regional lymph node areas in breast radiation therapy.

Methods: The realization of the new guidelines was a step by step process that started with multiple expert meetings where the existing guidelines were analyzed and the delineations of the lymph node regions were performed together with a surgeon, specialized in the anatomy of the drainage of the breast.

Results: The delineation guidelines are vessel-based. Since the occurrence of pathological lymph nodes is typically around the veins, the cranial and caudal borders of all different nodal regions are based on a 5 mm margin around the veins, except for the parasternal lymph node area. Compared to the existing guidelines there are some major changes.

Conclusion: With this project a national as well as a European (ESTRO) consensus guideline for the delineation of the regional lymph node areas in breast RT is reached. The new delineation atlas is vessel-based and no longer field-based.

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Radiotherapy (RT) has a major role in the treatment of breast cancer (BC). Adjuvant RT to the breast, thoracic wall and/or loco-regional lymph node areas has shown to significantly reduce local failure and improve overall survival [1,2]. Moreover, the data of the EORTC-22922 trial, the interim analysis of the MA.20 and the DBCG IMN study (L. Thorsen et al., manuscript in preparation) are supporting regional lymph node irradiation in all node positive BC patients [3–6]. These recent publications enhanced the interest of the radiation community in the development of innovative techniques for nodal irradiation in BC patients in order to decrease the doses to the adjacent normal tissues, especially to the lungs and heart. In the last 10 years the treatment techniques for BC RT evolved with good coverage and dose homogeneity of the target volumes and lower doses to the organs at risk (OAR). Most attention has been attributed to the development of new positioning systems, beam arrangements and respiratory motion management but an important step of the RT process has been neglected, being the improvement of the delineation quality of regional nodal volumes on the treatment planning computed tomography (CT) scan

[7–9]. Up to 10 years ago, there was no need for target volume delineation because the treatment fields were defined using fluoroscopy based on anatomical landmarks. With the introduction of CT-scan, an individualized conformal treatment plan in 3-Dimensions (D) can be made based on the delineations of the target volumes and the OAR. Inaccuracies in these delineations cause systematic errors in dose delivery that are repeated at each treatment fraction. Consequently, the potential advantage of implementing more complex treatment techniques can be jeopardized by incorrect delineations of the target volumes.

When evaluating the existing delineation policies following concerns arise. First, existing guidelines for target delineation in BC RT often use bony landmarks [10–13]. The bony structures that define the target boundaries are chosen to mimic the field boundaries of conventional 2D-radiation fields and have the advantage that they are well known and easy to recognize by radiation oncologists, but their relation with the lymphatics is not always straightforward. Moreover, adding margins from clinical target volume (CTV) to planning target volume (PTV) may result into larger volumes than treated with conventional 2D RT. Second, delineating the target volumes on CT-scan, especially the regional lymph node areas, did not appear that easy and results in a high interobserver and intercenter variability [14]. This may be due to

* Corresponding author at: Department of Radiation-Oncology, University Hospitals of Leuven, Herestraat 49, 3000 Leuven, Belgium.

E-mail address: karolien.verhoeven@uzleuven.be (K. Verhoeven).

a lack of consistency and interpretability of the existing guidelines and insufficient knowledge of the anatomy of the lymphatics of the breast. Third, different guidelines for the delineation of the regional lymph node areas exist [10–13]. Applying these guidelines do not result in same target volumes and there are no clear criteria to select the 'best guideline'.

Therefore, an evident need exists to optimize the guidelines for the delineation of the regional lymph node areas and to provide a good quality delineation atlas.

For this reason a national quality assurance project for breast RT in Belgium was started, named PROCAB (PROject of CAncer of the Breast). The first objective was to reach a national consensus guideline for the delineation of the regional lymph node areas in breast RT.

Methods

The realization of the new delineation guidelines was a step by step process, which took us almost 2 years. It started with multiple expert meetings where the existing guidelines were analyzed and the delineations of the lymph node regions were performed. The expert team consists of radiation-oncologists from different (mainly university) hospitals throughout Belgium, specialized in BC RT. Initially, the idea was to create simple guidelines using muscles and bony structures that are easy to recognize on a CT-scan. Due to ambiguities and differences in interpretability in the existing guidelines, target delineation resulted in unequal volumes. The nodal anatomy as well as the areas of regional recurrences were thoroughly studied. The breast surgeons explained the axillary dissection. Radiologists visualized the different vascular and muscular structures of the regional lymph node areas on CT-scan images. And finally, Prof. Lengelé, an anatomist and plastic surgeon involved in complex breast surgery, shared his expertise in the anatomy and lymphatic drainage of this region.

We realized that guidelines based on bony and muscular structures had different drawbacks: (1) the target volumes change with different treatment positions, arm position and patients' anatomy, (2) irradiated volumes increase in comparison to conventionally treated volumes in the 2D era and (3) the bony landmarks used for field boundaries have often no anatomical relation with the lymphatics. Therefore, our philosophy gradually changed, knowing that lymphatics run along the veins and that all regional nodal areas are connected to each other. Together with Prof. Lengelé, the regional lymph node areas were delineated again taking into account that new philosophy and by adding a 5 mm security margin around the veins.

The basis of the new delineation atlas was established. To confirm the validity of the guidelines, two university centers retrospectively analyzed the regional recurrences of formerly treated BC patients to verify where regional recurrences occur. Twenty regional recurrences of 3132 patients treated for early-stage breast cancer were observed. All, except for 2 internal mammary lymph node (IMN) recurrences, were axillary recurrences (levels I–III). So, no recurrences above/cranially of the subclavian artery arch or beyond the medial border of the internal jugular vein were seen.

The delineation atlas was checked by the same surgeon and also by radiologists. On a national consensus meeting, the delineation guidelines and atlases were proposed. Radiation-oncologists, specialized in BC RT of all 25 Belgian RT centers and Luxembourg were present and discussed the guidelines. After the meeting, minor modifications were performed to reach a national consensus. The very last corrections were inserted after merging our national consensus with the ESTRO group (breast/chest wall and nodal RT) during live meetings and additional discussions (B. Offeren et al., manuscript in preparation).

Results

For the delineation of the regional lymph node areas in breast RT the guidelines are based on the anatomy of the vessels because recurrences appear around the veins [normal anatomy and retrospective (unpublished) findings]. Therefore, the treated volume should be the perivenous region. Some basic principles are applied to determine the cranial and caudal borders of all different nodal regions, except for the IMN area. The cranial border is the top of the artery, because the artery is always located cranial to the vein. The caudal border is 5 mm below the caudal border of the vein. For the IMN region, there is a cranial–caudal gap of a few centimeters separating the vein and the artery, especially on the right side, because the external mammary vein drains into the brachiocephalic vein and the artery emerges below the arch of the subclavian artery. In clinical practice the IMN and the supraclavicular (SC) region (=level 4) are often treated together (5). Therefore, the cranial border of the IMN region corresponds to the caudal border of the SC region. The caudal limit of the IMN region is the cranial edge of the 4th rib. Most recurrences occur within the first three intercostal spaces [15].

The junctions between the different regions are defined using the relationship between the vessels and the natural barriers, such as muscular and bony structures. Bony structures, muscles and the pleura are also used as borders in order to prevent fatty tissue being treated (for example the anterior-external border of the level I; Fig. 1).

The delineation guidelines for the regional lymph node areas are created for determining the target volumes for elective nodal irradiation in stage I–II BC. However, they can serve as a base for the treatment of locally-advanced BC, but the target volumes should be adapted taking into account all the clinical and radiological information at initial diagnosis. The guidelines, described in detail below, are depicted in Tables 1 and 2. Delineation atlases are available on www.abro-bvro.be.

Supra- and retroclavicular region or level IV: CTVn_L4

The cranial border of level IV is the cranial edge of the subclavian artery arch (Fig. 2). When the subclavian artery runs toward the axillary regions, it makes a kind of bending/arch. It is just at the top of this arch the delineation should start. The caudal border of this region is defined 5 mm caudally of the caudal edge of the junction of the subclavian vein and the internal jugular vein. The medial border includes the medial edge of the internal jugular vein without any margin, excluding the carotid artery and thyroid

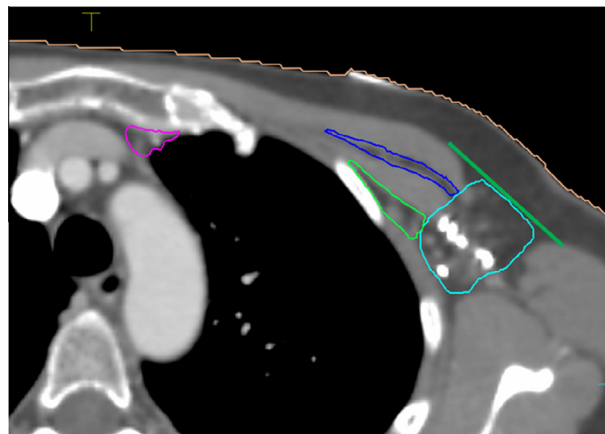


Fig. 1. Anterior-external border of level 1 of the axilla.

Table 1

PROCAB/ESTRO delineation guidelines for the clinical target volume (CTV) definition for elective irradiation of lymph node levels 2–4, interpectoral and internal mammary node region in breast cancer.

	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Level IV CTVn_L4	Cranial edge of the subclavian A. arch	5 mm caudal of the junction of the subclavian and the internal jugular vein	*Cranially: dorsal surface of the SCM *Caudally: the infrahyoid muscle (strap muscles) and clavicle	*Cranially: ventral edge of the subclavian artery *Caudally: lung	*Cranially: lateral border of the anterior scalene m. *Caudally: joining CTVn_L3, excluding the subclavian A.	The medial edge of the internal jugular vein, without any margin medially, excluding the carotid A. and thyroid gland
Level III of the axilla CTVn_L3	When the subclavian A. exits the thorax (crosses the vertical line between the clavicle and the first rib) and becomes the axillary A.	5 mm below the axillary vein when it crosses the medial border of the pectoralis minor m.	Posterior surface of the pectoralis major m. and the clavicle	Ribs and intercostal muscles. Try to exclude the brachial plexus if visible	Medial border of the pectoralis minor m.	Clavicle and/or lateral border of CTVn_L4
Level II of the axilla CTVn_L2	When the axillary A. crosses the medial edge of the pectoralis minor m.	5 mm below the axillary vein when it crosses the lateral border of the pectoralis minor m.	Dorsal surface of the pectoralis minor m.	Ribs and intercostal muscles	Lateral border of the pectoralis minor m.	Medial border of the pectoralis minor m.
Rotter or interpectoral space	Idem CTVn_L2	Idem CTVn_L2	Dorsal surface of the pectoralis major m.	Ventral surface of the pectoralis minor m.	Lateral border of the pectoralis major m.	Idem CTVn_L2
Internal mammary node region CTVn_IMN In	In conjunction with the caudal edge of CTVn_L4	Cranial edge of the 4th rib	*Cranially: manubrium Sterni *Caudally: the dorsal surface of the intercostal muscles	5 mm fatty space dorsal of the IM vessels, excluding the pleura	5 mm lateral of the IM vessels	*Cranially: lateral border of the brachiocephalic Vein* Caudally: up to the sternal bone

Abbreviations: SCM = sternocleidomastoid muscle; A. = artery; m. = muscle, IM = internal mammary.

Table 2

PROCAB/ESTRO delineation guidelines for the CTV for elective irradiation of lymph node level 1 in breast cancer.

	Cranial	Caudal	Anterior and external	Anterior and internal	Posterior
Level I of the axilla CTVn_L1	The top of the axillary artery where it crosses the lateral edge of the pectoralis minor muscle or 5 mm above the axillary vein, including clips and seroma	Around 4th–5th rib and guided by the clips and/or seroma if present	Not external to the ‘imaginary’ line between the anterior surface of pectoralis major muscle and latero-anterior border of the deltoid muscle (cranially) and the latissimus dorsi muscle (caudally), but include seroma and/or clips	Lateral border of the pectoralis major and minor muscle and the thoracic wall	Up to the ‘imaginary line’ connecting the anterior border of the subscapular m and the anterior border of the deltoid or latissimus dorsi muscle, so excluding the subscapular vessels

gland. The lateral border is cranially the lateral border of the anterior scalene muscle. Caudally the lateral border is in conjunction with the medial border of axillary level III (behind the clavicle), but excluding the subclavian/axillary artery. The anterior border is cranially the dorsal surface of the sternocleidomastoid muscle and more caudally the infrahyoid muscles (also strap muscles) and the clavicle. The posterior border is cranially the ventral surface of the subclavian artery, except if the distance between the dorsal surface of the internal jugular vein and the ventral edge of the subclavian artery is more than 1 cm. In that case, the posterior border stops at 1 cm posteriorly of the dorsal surface of the internal jugular vein. Caudally the posterior border is the pleura.

Axillary level III or the infraclavicular fossa: CTVn_L3

The cranial border of level III starts when the subclavian artery exits the thorax (i.e. when it crosses the ‘imaginary’ vertical line drawn between the clavicle and the first rib) and becomes the

axillary artery (Fig. 3A). The caudal border of this level is 5 mm below the axillary vein where it crosses the medial border of the pectoralis minor muscle. The medial border is defined by the clavicle and/or the lateral border of the junction of the subclavian vein and the internal jugular vein (=in conjunction with the lateral border of the SC region). The lateral border of level III is the medial border of the pectoralis minor muscle. The anterior border is determined by the dorsal surface of the pectoralis major muscle and the clavicle. Posteriorly the border of level III is defined by the ventral surface of the ribs and intercostal muscles. Try to exclude the brachial plexus if visible and located more than 5 mm from the vein.

Axillary level II: CTVn_L2

The cranial border of level II starts as the axillary artery crosses the medial edge of the pectoralis minor muscle (Fig. 3B). The caudal border is 5 mm below the axillary vein when it crosses the lateral border of the pectoralis minor muscle. Medial and

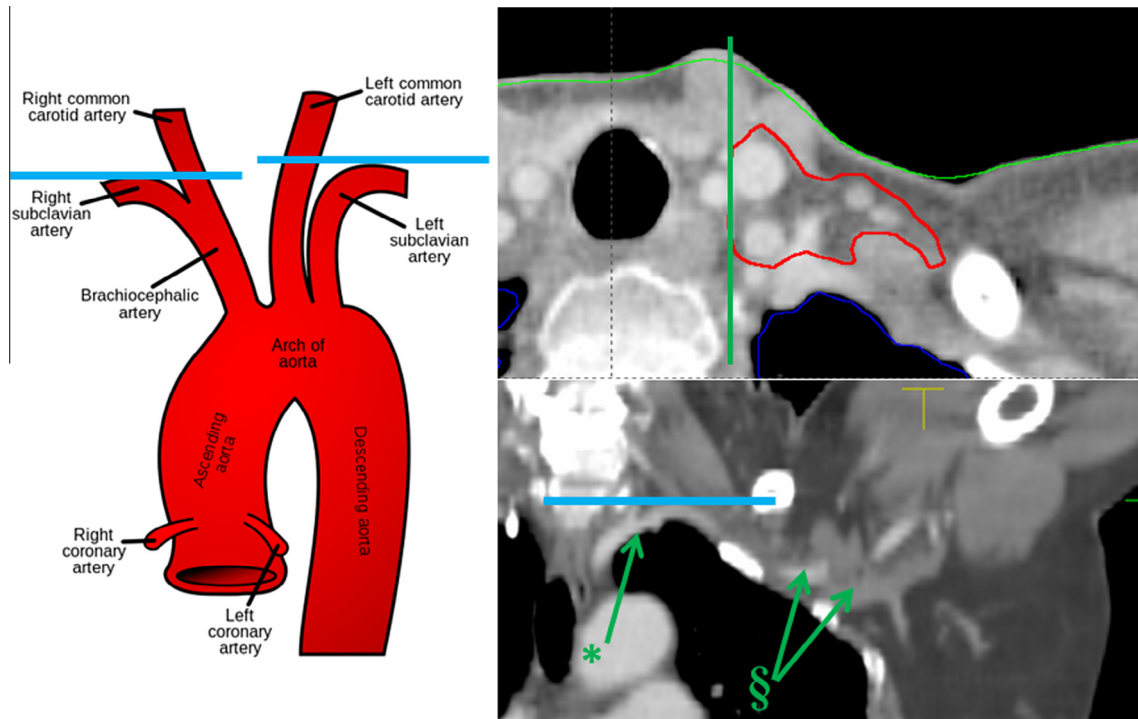


Fig. 2. The cranial border of level 4 or the supraclavicular region. *Subclavian artery arch. §Axillary artery and vein.

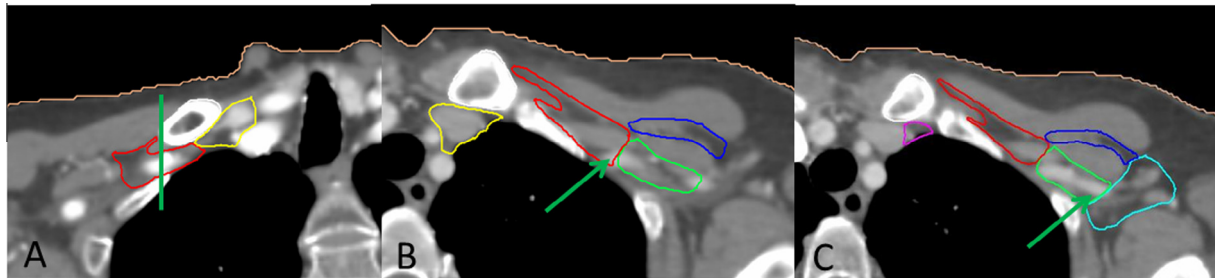


Fig. 3. Cranial border of level 3 (A), level 2 (B) and level 1 (C) of the axilla.

lateral border of level II is defined by the medial and lateral border of the pectoralis minor muscle. The anterior border is the dorsal edge of the pectoralis minor muscle and the posterior border is up to the ribs and intercostal muscles. Try to exclude the brachial plexus.

Rotter or interpectoral space

The rotter space is a secondary drainage of the breast and lies in between the two pectoralis muscles. The cranial, caudal and medial borders are the same as of level II. The lateral border is determined by the lateral border of the pectoralis major muscle (and not the pectoralis minor muscle as in level II). Anteriorly, the border is the dorsal surface of the pectoralis major muscle and posteriorly the ventral edge of the pectoralis minor muscle.

Axillary level I: CTVn_L1

The cranial border of level I begins at the top of the axillary artery when it crosses the lateral border of the pectoralis minor muscle, including the clips and seroma if present, and avoiding the humeral vessels (Fig. 3C). The caudal border of level I is around the 4th–5th rib on the mid axillary line, i.e. the level at which the

lateral border of the pectoralis major muscle merges to the ribs. The anterior-external border is set by the ‘imaginary’ line between the anterior surface of the pectoralis major muscle and the latero-anterior border of the deltoid muscle (cranially) or the latissimus dorsi muscle (caudally), but including seroma and/or clips. The anterior-internal border is determined by the lateral border of the pectoralis major and minor muscle and the thoracic wall. Posteriorly, the border is the ‘imaginary’ line connecting the anterior edge of the subscapular muscle and the anterior border of the latissimus dorsi muscle and so excluding the subscapular vessels which are responsible for the drainage of the back.

Internal mammary node region: CTVn_IMN

The cranial border of the IMN region is in conjunction with the caudal border of the SC region/level IV. The caudal border of this region ends at the cranial edge of the 4th rib. The medial border of this region is defined cranially by the lateral border of the brachiocephalic vein and caudally by 5 mm medial of the internal mammary (IM) vessels. The lateral border of the IMN region is 5 mm lateral of the IM vessels. The anterior border is cranially determined by the manubrium sterni and caudally by the dorsal surface of the intercostal muscles, including the perivascular fatty

space. For the posterior border 5 mm of fatty space is taken posteriorly of the IM vessels, but excluding the pleura.

Discussion

Breast radiation therapy plays an important role in the treatment of breast cancer. The life expectancy in BC patients has improved and approximately 75% of the BC patients can actually be cured.

Regional nodal irradiation (RNI) in node positive patients or in patients with medially or centrally located tumours improves the disease free and metastasis free survival with a trend in an overall survival gain [3–6], although the doses to the OAR, i.e. the lungs and the heart, are increasing with RNI. With the evolution of more complex treatment techniques, it is possible to spare the OAR more while preserving the target volume coverage. However, to maximally benefit from these technical improvements the definition of the target volumes should be more precise.

Therefore, a national consensus guideline for the delineation of the regional lymph node areas in breast RT is introduced. The guidelines are based on the anatomy of the blood vessels, rather than on bony structures, because the lymphatics run along the veins [16]. The advantages of using the veins to guide our target are multiple. First, it is more patient-tailored and precise, because the anatomy of patients can differ a lot. Second, the treated volumes will not be larger than treated with conventional radiotherapy. Third, it is applicable independent of the treatment position. Fourth, exclusion of the scapulo-humeral joint (SHJ) to prevent shoulder problems is almost never an issue. In the rare case the target volume lies close to the SHJ, the balance should be made between the risk of regional recurrence and possible shoulder problems.

The delineation guidelines are described meticulously and supported by a clear delineation atlas using a CT-scan with 3 mm slice thickness and an atlas where the normal anatomy, needed for the delineation of the regional lymph node areas, is delineated. Clear guidelines, continuous education of professionals and extensive quality control have shown to reduce the interobserver and inter-center variability in target delineation, as was described for rectal cancer radiotherapy by Joye et al. [17].

These new guidelines are introduced because there is an urgent need to update the existing guidelines and especially to reach a consensus. Together with ESTRO a European consensus guideline for the regional lymph node regions is obtained. Tables 1 and 2 describe the same volumes as explained by ESTRO, but in a somewhat different text to add complementary information to the ESTRO consensus for an even better understanding (ESTRO manuscript, B. Offersen et al., in preparation). This consensus is important not only to allow comparison of treatment techniques and dosimetric studies with each other but also for improving the quality in breast radiation therapy by standardizing the target volumes.

The largest difference with the existing guidelines is the cranial border of the SC region. It is not the caudal border of the cricoid bone anymore, but the top of the subclavian artery arch. Another important difference is that the target volume is concentrated 5 mm around the veins and is not defined by muscles and bony structures. A coronal view is very helpful to evaluate the target volume.

The presented new guidelines have some limitations. First, the discrimination of the vein and the artery is not always easy. The use of IV contrast substantially facilitates the delineation process, however it is not mandatory. At the beginning it can serve for learning purposes, especially if natural fatty contrast is scarce. Second, the atlas is not validated. But retrospective analyses of nodal involvement and regional recurrences in patients treated in the

past for early stage breast cancer were performed in two Belgian university centers and confirmed that regional recurrences occur around the veins and not between the subclavian artery arch and the cricoid bone. These findings were also confirmed by the ESTRO team.

A consequence of the new guidelines is that there may exist a gap between the cranial border of the CTV breast or chest wall and the caudal border of the CTVn_L1–4. This is relatively new, but in fact because of the lymphatic pathway, it is not part of the target volume.

In conclusion, a national quality assurance project for breast RT in Belgium, PROCAB, was started. The first objective of this project was to obtain a national and recently also a European consensus guideline for the delineation of the regional lymph node regions. The guidelines are vessel-based with a major change in the cranial border of the supraclavicular lymph node region compared to the existing guidelines.

Further perspectives of the project will be to study the effect of central review on the interobserver variability and so also the quality of the delineation of the regional lymph node region. Therefore, the PROCAB study will serve as an additional validation of the guidelines in the future.

Conflict of interest statement

None.

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