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Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: National guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group

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Abstract

During the past decade planning of adjuvant radiotherapy (RT) of early breast cancer has changed from two-dimensional (2D) to 3D conformal techniques. In the planning computerised tomography (CT) scan both the targets for RT and the organs at risk (OARs) are visualised, enabling an increased focus on target dose coverage and homogeneity with only minimal dose to the OARs. To ensure uniform RT in the national prospective trials of the Danish Breast Cancer Cooperative Group (DBCG), a national consensus for the delineation of clinical target volumes (CTVs) and OARs was required. *Material and methods.* A CT scan of a breast cancer patient after surgical breast conservation and axillary lymph node (LN) dissection was used for delineation. During multiple dummy-runs seven experienced radiation oncologists contoured all CTVs and OARs of interest in adjuvant breast RT. Two meetings were held in the DBCG Radiotherapy Committee to discuss the contouring and to approve a final consensus. The Dice similarity coefficient (DSC) was used to evaluate the delineation agreement before and after the consensus. *Results.* The consensus delineations of CTVs and OARs are available online and a table is presented with a contouring description of the individual volumes. The consensus provides recommendations for target delineation in a standard patient both in case of breast conservation or mastectomy. Before the consensus, the average value of the DSC was modest for most volumes, but high for the breast CTV and the heart. After the consensus, the DSC increased for all volumes. *Conclusion.* The DBCG has provided the first national guidelines and a contouring atlas of CTVs and OARs definition for RT of early breast cancer. The DSC is a useful tool in quantifying the effect of the introduction of guidelines indicating improved inter-delineator agreement. This consensus will be used by the DBCG in our prospective trials.

The first national guidelines for adjuvant radiotherapy (RT) of breast cancer in Denmark were made by the Danish Breast Cancer Cooperative Group (DBCG) in 1977. Until 2006 the majority of patients referred for postoperative RT were treated using two- or three-field techniques planned on a simulator guided by external markers and bony landmarks. Typically the treatment technique after breast conserving surgery or mastectomy included an anterior field against the lymph nodes (LN) in the clavico-axillary

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region in combination with tangential opposed fields to the breast region. In case of postmastectomy irradiation an electron field was often used to the chest wall [1]. Patients treated with this technique had a significantly lower loco-regional recurrence (LRR) rate and improved overall survival compared to non-irradiated patients [2–4]. Since 2003 a gradual change in treatment planning from two-dimensional (2D) to computed tomography (CT)-based 3D was made in Denmark, thus the DBCG Radiotherapy Committee in 2006 revised the guidelines for post-mastectomy RT to include treatment based on a CT scan [5]. Shortly after, CT-based planning after breast conserving surgery was also introduced and since 2007 3D planning has been the national standard for all patients treated with adjuvant breast RT in Denmark.

The purpose of introducing CT-based target delineation was to optimise clinical target volumes (CTV) dose coverage and homogeneity and minimise organs at risk (OAR) dose. Since data from patients treated during the period with 2D planning has demonstrated a very low risk of LRR after adjuvant RT, it was important to assure that no significant change in the field arrangements and/or sizes of the fields during the shift from 2D to 3D was introduced. Other groups have proposed institutional guidelines for target definition in adjuvant breast cancer RT [6–10], but to our knowledge no national guidelines have been presented. In the DBCG Radiotherapy Committee we monitor the LRR rates in all patients treated with adjuvant RT and we initiate prospective national RT protocols. It is therefore important to reach a national consensus on target delineation in order to minimise contouring uncertainty and maximise a uniform treatment planning. The aim of the present study was to provide the first Danish consensus on delineation of CTVs and OARs in adjuvant breast RT to be used for patients treated according to the DBCG guidelines.

Material and methods

A series of national workshops with the participation of radiation oncologists and medical physicists experienced in adjuvant breast RT from each of the eight Danish RT centres was held between 2010 and 2012. During multiple dummy-runs CTVs and OARs delineation was performed by seven radiation oncologists on a contrast enhanced planning CT scan of a 62-year-old woman operated for a screening-detected right-sided breast cancer with microscopically radical breast conservation and level I–II axillary clearance. The mammography (Figure 1) identified a tumour at 1 o´clock 6 cm from the papillary complex. The tumour bed was marked intra-operatively with four metallic clips. Pathological tumour size was 13 mm, invasive ductal carcinoma, malignancy grade 1, 100% eostrogen receptor positive, HER2 negative, and there were two macrometastases among the 14 axillary LN removed. The patient was positioned supine in treatment position with both arms symmetrically abducted approximately 120° in a breast board Civco™ (Medtec) and with the sternal bone in horizontal position. The palpable breast was demarcated with a radiopaque wire. Another wire was placed cranio-caudally in the midsternal line and one on the surgical scar. Intravenous contrast was administered immediately prior to scanning. The scan was acquired during free breathing, and covered the area from the mid-neck to the upper abdomen with a slice thickness of 2 mm. Delineation of anatomical structures was performed by experienced oncologists (one from each seven Danish RT centre and one representing two centres) using either the Eclipse™ (Varian Medical Systems Inc.), Oncentra External Beam™ (Nucletron, An Elekta Company) or Pinnacle™ (Philips) treatment planning systems. The following CTVs were delineated: breast, tumour bed, axillary LN (level I, II and III), the periclavicular LN (medial supraclavicular, lateral supraclavicular and infraclavicular), the internal mammary LN and the interpectoral LN. The following OARs were delineated: heart, left anterior

Figure 1. The mammography identified a tumour at 1 o´clock 6 cm from the papillary complex in the right breast.

descending coronary artery (LADCA), ipsilateral lung, larynx and spinal cord. Delineations of the lung and spinal cord were performed by an automatic contouring function, and corrected manually if needed.

Delineation was performed prior to the workshops to facilitate the discussion process to reach the final consensus.

During the meetings guidelines for target delineation in patients operated with mastectomy were also discussed, so we provide our guidelines for delineation of the chest wall too.

The resulting national guidelines and atlas were approved by the DBCG Radiotherapy Committee. Only the delineation of CTVs in a standard patient will be described in this article, since the definition of the planning target volume depends on institutional guidelines.

The same oncologists delineated CTVs and OARs according to the consensus guidelines, approximately six months after the national delineation consensus was approved.

Delineation similarities before and after the consensus among the individual delineation were evaluated using the Dice similarity coefficient (DSC). DSC is defined as the intersection volume between volume A and (a reference) volume B divided by the mean of volumes of A and B [11,12]. Hence the coefficient is confined to the interval [0;1] and a DSC close to 0 or 1 indicates no or perfect overlap with the reference structure, respectively. The consensus delineated CTVs and OARs all served as reference volumes when calculating the DSC. The DSC was not calculated for the LADCA (often the LADCA cannot be visualised on a planning CT scan due to motion of the heart), lung or spinal cord (since the latter are contoured automatically).

Results

Preconsensus delineation

During the first dummy-run all participating centres submitted a set of delineated breast and lymph node targets as well as risk volumes. A representative example of the delineations performed is shown in Figure 2A and B. It documents clinically relevant differences in the delineated volumes. Thus, a national consensus was needed.

Consensus delineation

Figure 3 shows representative examples of CTVs and OARs from the consensus delineation. The full CT atlas with all consensus delineations is available online (http:// www.dbcg.dk : Retningslinjer/Vejledninger). The guidelines for delineation describing the anatomical boundaries for each CTV and OAR both after breast conserving operation and mastectomy are shown in Table I.

Constraints used by DBCG

During dose planning we strive to achieve a dose distribution in the CTV breast or CTV chest wall of

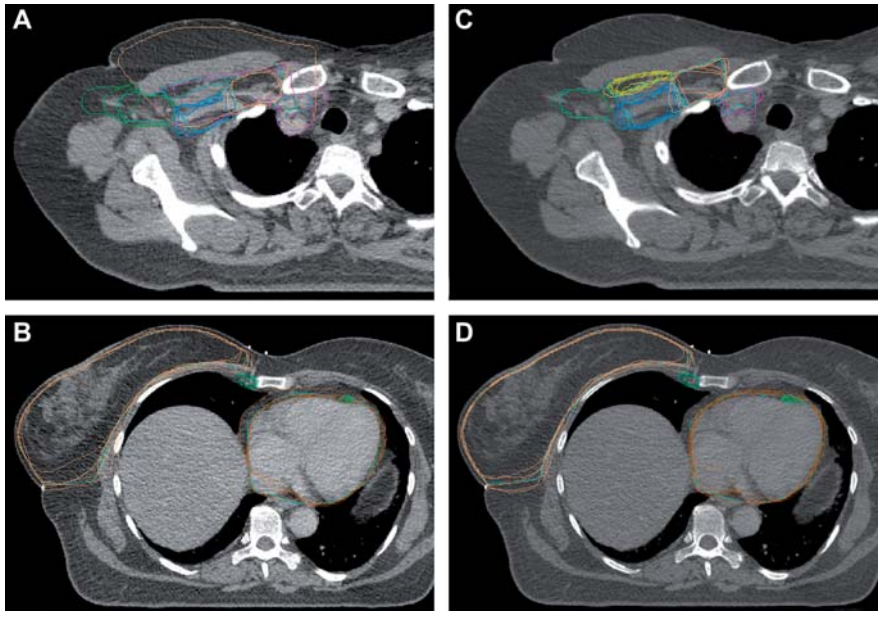

Figure 2. Representative examples of preconsensus and postconsensus delineations. A and B: (to the left) Preconsensus delineations. C and D: (to the right) Postconsensus delineations. CTV-breast: orange, CTV axillary LN level I: bright green, CTV axillary LN level II: blue, CTV axillary LN level III: orange, CTV interpectoral LN: yellow, CTV periclavicular LN: pink, CTV IMN: forest green.

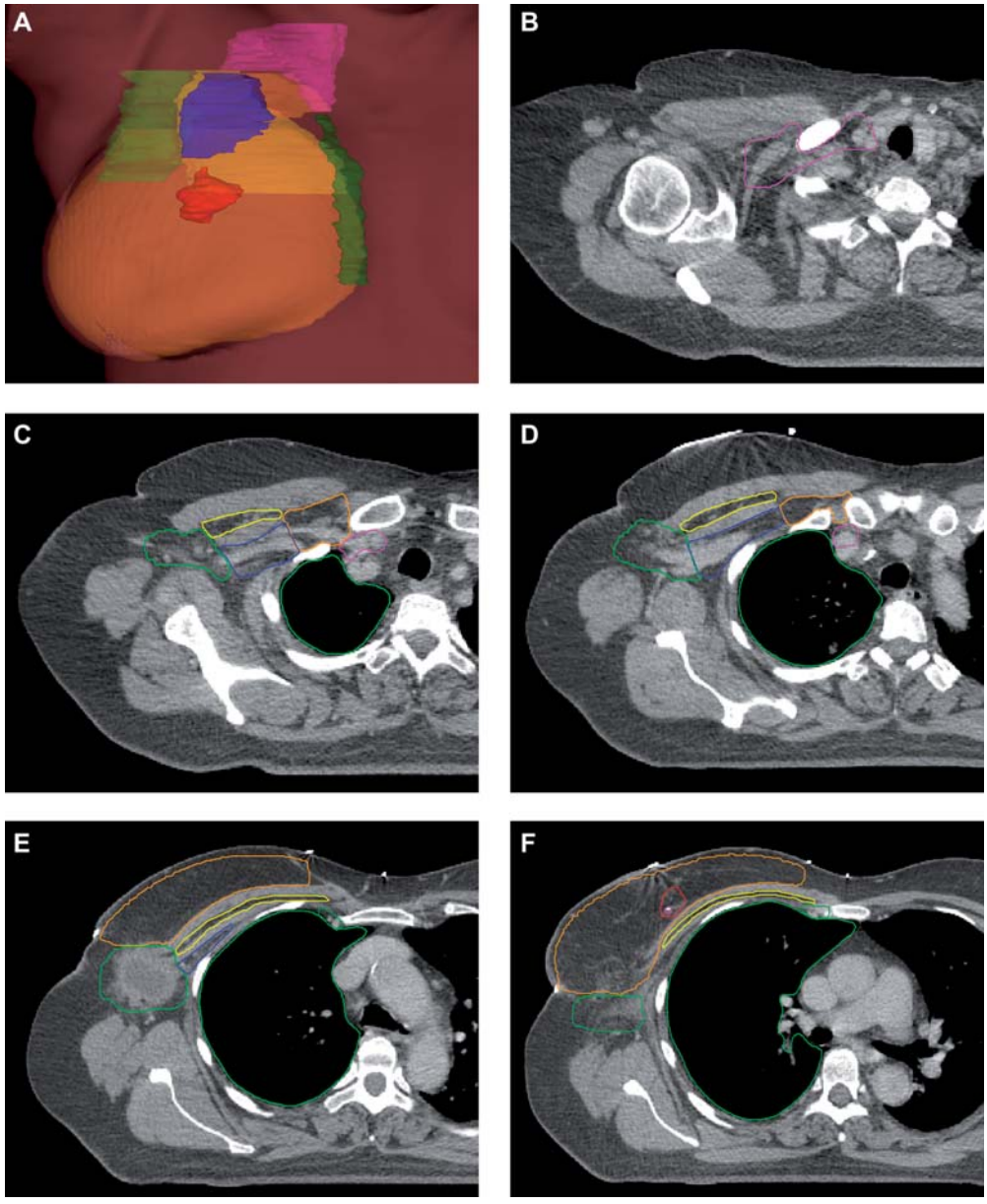

Figure 3. Representative examples of CTVs from the consensus delineation. The full CT atlas is available online (http:// www.dbcg.dk : Retningslinjer/Vejledninger). CTV- breast: orange, Tumour bed: red, CTV axillary level I: bright green, CTV axillary level II: blue, CTV axillary level III: orange, CTV interpectoral LN: yellow, CTV IMN: forest green, CTV periclavicular LN: pink, Ipsilateral lung: green.

95–107% (normofractionated RT) according to the ICRU criteria [13]. For RT of lymph nodes we accept a dose distribution within the range of 90–107%. If the dose inhomogeneity is higher than 107% it is recommended to lower the total dose to avoid *double trouble*. It has high priority to spare the OAR as much as possible from radiation, and our constraints are shown in Table II. The priorities are:

> CTV-boost > LADCA > heart > lung > CTV-breast/chest wall > CTV-periclavicularis > CTV-IMN > contralateral breast.

Postconsensus delineation

During a second dummy-run six months after the approval of the national delineation guidelines a new delineation set was submitted by all eight centres. A representative example of the delineations performed postconsensus is demonstrated in Figure 2C and D. It shows a higher degree of contouring agreement among the RT centres. Averages and ranges of the DSC are presented in Table III for the relevant regions of interest (ROIs). For all ROIs the DSC improved after consensus. It was proposed by Zijdenbos et al. that a coefficient larger than

Table I. The national guidelines for delineation of target volumes in adjuvant radiotherapy of early breast cancer.

DCBG guidelines for delineation of CTV of breast and CTVs of the regional lymph node regions						
LN region	cranial	caudal	ventral	dorsal	lateral	medial
Breast Residual breast, including tumour bed	Maximal to the caudal edge of the sterno-clavicular-junction	The intermammary sulcus	5 mm below the skin	M. pectoralis major	The axillary vessels (branches from the lateral thoracic vessel)	Maximal to the ipsilateral edge of sternum
Regio mammaria (PMRT)	Equal to a CTV-breast guided by the contralateral breast					
CTV-boost	Tumour bed including clips and seroma plus 5 mm's margin					
Level I	1 cm below caput humeri	Free edge of m. pectoralis major including seroma	5 mm below the skin	M. latissimus dorsi, 5 mm dorsal of the axillary vessels	Maximal to 5 mm below the skin	CTV-breast, lateral border of m. pectoralis minor, m. biceps brachii
Level II	5 mm cranial to the axillary vessels	Caudal edge of m. pectoralis minor	Dorsal surface of m. pectoralis minor	Chest wall, 5 mm dorsal of the axillary vessels	Lateral border of m. pectoralis minor	Medial border of m. pectoralis minor
Level III	5 mm cranial to the axillary vessels	1 cm caudal to the axillary vessels	Dorsal surface of m. pectoralis major	Chest wall, 5 mm dorsal of the axillary and subclavian vessels	Medial border of m. pectoralis minor	Clavicle
Periclavicular	Caudal edge of cricoid cartilage	Cranial border of level II and III (lateral). Cranial edge of the sterno-clavicular-junction (medial)	Dorsal surface of m. sternomastoideus, dorsal surface of clavicle, 5 mm below skin	In front of the clavicle, behind a. carotis interna, in front of m. scalenus ant, m. scalenus med, m. omo-hyoideus and m. levator scapulae	Medial edge of m. pectoralis minor, clavicle	Medial edge of a. carotis interna and v. jugularis interna
Interpectoral	Cranial border of m. pectoralis minor	Caudal border of m. pectoralis minor	Dorsal surface of m. pectoralis major	Ventral surface of m. pectoralis minor	Lateral border of m. pectoralis minor	Medial border of m. pectoralis, if possible to the edge of sternum
IMN	Cranial edge of costa 1	Cranial edge of costa 5	Dorsal surface of m. pectoralis major, dorsal surface of sternum	Pleura	5 mm lateral of internal mammary vessels or 2 cm from the edge of sternum	The edge of sternum

0.70 represents a good overlap [14]. This was accomplished by the average DSC for only two of eight ROIs before but for seven of nine ROIs after consensus.

Discussion

Postoperative loco-regional RT in patients with early breast cancer has shown a significant benefit in lowering the risk of loco-regional failures and death from breast cancer both after breast conserving surgery and mastectomy [2–4,15,16]. This fundamental knowledge was acquired during the era of simple 2D planned RT. Today's CT planned 3D conformal RT enables the precise volumetric and geographical definition of CTV as well as OAR. Deijkema et al. [8] were pioneers in describing the anatomical borders of the different loco-regional lymph node areas in planning CT scans, however, using these guidelines we observed an unwarranted increase in the irradiated volumes compared to the volumes used in the days of 2D planning.

Table II. Constraints for organs at risk in adjuvant radiotherapy of early breast cancer.

Organ at risk	Normofractionation 2 Gy per fraction/ 5 fractions/week
LADCA	$V_{20Gy} = 0\%$
Heart	$V_{20Gy} = 10\%, V_{40Gy} = 5\%$
Ipsilateral lung	$V_{20Gy} = 25\%$ (exclusive periclavicular LN) $V_{20Gy} = 35\%$ (inclusive periclavicular LN) Mean dose < 18 Gy
Spinal cord	Max. 45 Gy
Plexus brachialis	Max. 54 Gy
Maximal dose of CTV	107% = 53.5 Gy
Maximal dose outside PTV	54 Gy

CTV, clinical target volume; LADCA, left anterior descending coronary artery; LN, lymph nodes; PTV, planning tumor volume.

Breast, tumour bed and chest wall

In the postlumpectomy situation the CTV breast includes all mammary glandular tissue. The lateral border of the breast may sometimes be difficult to define in a planning scan of patients with gland involution. However, in most cases it is possible even in a scan without intravenous contrast to identify the small axillary vessels running in cranio-caudal direction. These vessels (the lateral thoracorsal vessel with the lateral mammary branches) may be used as a surrogate marker of the lateral border of the breast. Gland involution may also dim the cranial and medial borders of the breast; the inferior edge of the clavicle and the lateral edge of the sternum can be used as surrogate markers of the cranial and medial borders of the breast, respectively.

In the DBCG consensus the CTV boost is defined as the tumour bed expanded by 5 mm in all directions without exceeding the CTV breast. The tumour bed includes all surgically inserted clips and the solid tissue and/or seroma in-between. All relevant information from the preoperative mammography, ultrasound and in some cases MR mammography together with the description of the surgical procedure is used in the delineation of the tumour bed. During breast conserving surgery the Danish surgeons insert 4–6 clips in the lumpectomy cavity. In case of oncoplastic surgery the clips are inserted in the cavity before transposition of the breast tissue so the radiotherapist has to be aware of possible movement of the clips if a boost is planned. For mastectomy the borders of the CTV chest wall are guided by the position of the contra-lateral breast.

In case of bilateral mastectomy the caudal border is defined as 3 cm caudal of the mastectomy scar. The borders and the mastectomy scar are marked with radiopaque wires before the planning CT scan. The ventral border is 5 mm below the skin surface, except for a region 3 cm cranially and caudally to the mastectomy scar where a bolus of 3–6 mm thickness is applied to ensure adequate dose in the skin. Sometimes the mastectomy scar extends outside the breast region to achieve a good cosmetic result, however, only the part of the mastectomy scar inside the breast region is target as we do not consider tumour contamination to be a clinical problem. The dorsal border of the chest wall is the ventral side of the major pectoral muscle; if this is difficult to define the ribs can be used instead.

Regional LN

The exact border between two lymph node areas is in most cases not sharp. However, using more advanced field techniques such as intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) it is pivotal to avoid gaps between adjacent LN volumes to ensure homogenous dose in the intersection. Compared to the guidelines from other institutions [8,10] our consensus guideline for the interpectoral LN CTV results in a quite large volume [10]. Our rationale is to ensure treatment of the upper medial quadrant of the chest wall, particularly in the postmastectomy situation, as was the case during the era of 2D planning (to avoid a 'cold spot' in the dose planning).

Table III. Mean and ranges of DSC before and after consensus.

Volume	Consensus volume (ml)	Mean DSC (range) Before consensus	Mean DSC (range) After consensus
Breast	1247	0.93 (0.89–0.96)	0.95 (0.93–0.96)
Boost	40	NA	0.75 (0.60–0.89)
Internal mammary LN	15	0.59 (0.32–0.72)	0.71 (0.63–0.81)
Axillary LN level I	108	0.65 (0.59–0.75)	0.70 (0.60–0.77)
Axillary LN level II	32	0.56 (0.35–0.69)	0.76 (0.67–0.84)
Axillary LN level III	17	0.56 (0.39–0.73)	0.74 (0.66–0.82)
Periclavicular LN	47	0.41 (0.34–0.56)	0.56 (0.43–0.73)
Interpectoral LN	33	0.54 (NA)	0.66 (0.55–0.78)
Heart	731	0.91 (0.88–0.94)	0.94 (0.90–0.96)

DSC, Dice similarity coefficient; NA, not available.

In contrast to other institutional guidelines the DBCG consensus proposes to limit the posterior border of axillary LN to 5 mm dorsal to the axillary vessels. When using the CTV definitions by Dijkema [8] we observed that the irradiated volume increased compared to 2D planning. In our experience based on the 2D planning the risk of a regional recurrence in and posterior to level II after previous regional irradiation is very small (unpublished observations). Since part of the brachial plexus is located just posterior to the axillary vessels we find it important to be restrictive with the dose to this region to avoid later nerve morbidity.

In cases with severe lymph node involvement we include level I in the RT fields. The definition of 'severe involvement'is not exact. It is based on the decision of the clinician, however at least 50% of the removed LN should be tumour positive. The tradition in the 2D era was to limit the RT fields around the edge of the humeral head, and using 3D scans this corresponds to defining the cranial border of level I around 1 cm caudal to the humeral head to avoid later arm morbidity. Since the risk of recurrence in the posterior part of level I in our experience is very low, we exclude the most posterior part of this lymph node region positioned between the chest wall and the dorsal muscles.

In the days of 2D planning the periclavicular region was defined by a cranial border corresponding to the lower edge of the sixth cervical vertebra and a lateral border corresponding to two thirds of the length of the clavicle. Regarding the medial border most centres used the position of a wire following the anterior edge of the sternocledomastoideus muscle to spare the thyroid gland, eosophagus and larynx from a high dose. Based on this routine we recommend the exclusion of the most medial part of the periclavicular LN from the CTV. Caudally the periclavicular LNs meet the IMN behind the sternum and are here located so dorsally that this region may be excluded from the CTV to avoid excessive lung irradiation, taking in consideration that a large percentage of the patients have been treated with chemotherapy just prior to the RT and therefore have a larger risk of side effect.

OARs and constraints

The delineation of the heart and left anterior descending coronary artery (LADCA) is based on the guidelines from Feng [17] and is defined by the heart muscle including the complete pericardia from the lower part of the pulmonic trunc to the apex. By including the complete pericardia we insure that all coronary arteries are within the heart outline. LADCA is delineated from aorta including the left main artery to the cardiac apex cordis. It is often difficult to visualise the caudal part of the LADCA but here a surrogate is the interventricular gap.

Dice similarity coefficient (DSC)

As discussed earlier the DSC can readily be used as a measure of the overlap for larger volumes, but is not very useful for very small volumes; the use of the DSC as an absolute measure of overlap is also questioned by Zou et al. [18]. The consensus LADCA volume is only 5.4 cm^3 which means that no overlap in a few slices results in a low DCS although the exact position of the delineated LADCA may not differ significantly seen from a clinical point of view. Hence one needs to investigate the delineated volumes visually and not solely focus on the exact value of the average DSC. However, the DSC is a useful tool for evaluating the improvements in the workshop process especially for the larger volumes as listed in Table III.

Individualised dose planning

In most patients the radiation oncologist must balance the gain from lower risk of loco-regional recurrence with the cost of side effects from irradiating OAR. The therapy of early breast cancer patients is multimodal and complex, e.g. the systemic therapy both reduces the LRR risk and increases the risk of late morbidity after RT. It is also evident that the risk of late radiation morbidity is larger in patients operated with axillary lymph node dissection (ALND) compared to an operation based on the sentinel node technique [19]. When balancing the pros and cons for RT in the individual patient we also need to consider co-morbidity as an important factor, e.g. the risk of heart morbidity is significantly higher if the patient already has had a myocardial infarction [20]. In heavy smoking patients with lung diseases the field arrangement should be modified to spare as much lung tissue as possible from RT, and in some patients the RT may even cause more trouble than benefit to the patient. Thus, for example, some patients should be offered mastectomy instead of lumpectomy to avoid the adjuvant RT. In many patients treated with chemotherapy mucositis is a problem, thus the patients complain about problems with swallowing food during the last week of regional RT (unpublished observations). Since the risk of LRR in the most medial part of the medial supraclavicular region is very small it is in most patients justified to focus on sparing the eosophagus and larynx from RT [21].

Conclusion

As a consequence of shifting from 2D to 3D treatment planning we have witnessed an increase in the complexity of standard adjuvant RT of early breast cancer. We are now able to target the desired volumes more accurately because they can be visualised on the planning CT scan, however, the critical OARs are also visible and it is a challenge to spare them as much as possible from radiation dose. A national delineation guideline and contouring atlas helps in achieving more precise and uniform CTVs and this enables us to create more individualised treatment plans than previously. However, it is still very important to be aware of the techniques used and volumes treated in the days of 2D, since the far majority of today's knowledge of treatment outcome is based on those techniques. A solid delineation procedure for the breast, the involved LN and OARs is also needed for future rotational therapy as all target and risk volumes really need to be delineated.

The DBCG consensus guidelines presented in this article will be used in the future trials initiated by the DBCG RT committee, and they are already by now being used in the daily routine in Denmark. Follow-up will be made prospectively on a regular basis to ensure a quality control regarding the clinical impact of the new guidelines.

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