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Original Article

Proposal for the delineation of neoadjuvant target volumes in oesophageal cancer

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ABSTRACT

Purpose: To define instructions for delineation of target volumes in the neoadjuvant setting in oesophageal cancer.

Materials and methods: Radiation oncologists of five European centres participated in the following consensus process: [1] revision of published (MEDLINE) and national/institutional delineation guidelines; [2] first delineation round of five cases (patient 1–5) according to national/institutional guidelines; [3] consensus meeting to discuss the results of step 1 and 2, followed by a target volume delineation proposal; [4] circulation of proposed instructions for target volume delineation and atlas for feedback; [5] second delineation round of five new cases (patient 6–10) to peer review and validate (two additional centres) the agreed delineation guidelines and atlas; [6] final consensus on the delineation guidelines depicted in an atlas.

Target volumes of the delineation rounds were compared between centres by Dice similarity coefficient (DSC) and maximum/mean undirected Hausdorff distances (H_{max}/H_{mean}).

Results: In the first delineation round, the consistency between centres was moderate (CTVtotal: DSC = 0.59–0.88; H_{mean} = 0.2–0.4 cm). Delineations in the second round were much more consistent. Lowest variability was obtained between centres participating in the consensus meeting (CTVtotal: DSC: $p < 0.050$ between rounds for patients 6/7/8/10; H_{mean}: $p < 0.050$ for patients 7/8/10), compared to validation centres (CTVtotal: DSC: $p < 0.050$ between validation and consensus meeting centres for patients 6/7/8; H_{mean}: $p < 0.050$ for patients 7/10).

A proposal for delineation of target volumes and an atlas were generated.

Conclusion: We proposed instructions for target volume delineation and an atlas for the neoadjuvant radiation treatment in oesophageal cancer. These will enable a more uniform delineation of patients in clinical practice and clinical trials.

Oesophageal cancer is the seventh most common cancer worldwide and the sixth leading cause of cancer-related mortality [1]. Even though the standard treatment in locally advanced disease involves neoadjuvant chemoradiotherapy (nCRT) followed by surgery [2–5], there is no gold standard regarding the definition of the irradiation volume. In the past, trials have used various instructions for the target volume, which have rarely been described in detail [3,6–9].

The implementation of advanced radiotherapy techniques, such as intensity modulated radiotherapy (IMRT) and proton therapy allows us to reduce the dose to the organs at risk (OARs) by shaping the dose closer to the target volume [10–14]. A fair comparison of treatment outcome between various radiotherapy techniques across different centres requires, however, uniform guidelines for the delineation of the radiation target volume. Additionally, a poor

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delineation quality correlated with inferior outcome in other tumour sites, entailing a consistent delineation approach [15,16].

The aim of this study was to define a proposal for the delineation of the radiation target volume in the neoadjuvant setting in oesophageal cancer, including an atlas. These will be used in the PROton versus photon Therapy for Esophageal Cancer – a Trimodality strategy (PROTECT) trial, a multicentre international randomised phase III study of nCRT with protons versus photons in locally advanced oesophageal cancer, but could also benefit other clinical trials.

Materials and methods

Participating centres

This study was conducted within the PROTECT trial consortium. The general aim of the PROTECT trial is to reduce radiotherapy-related toxicity by replacing photons with protons in the neoadjuvant setting for locally advanced oesophageal cancer in a randomised phase III study. The working party of the delineation guidelines and atlas consisted of radiation oncologists specialised in upper gastro-intestinal cancer at the University Hospitals Leuven (BE), Aarhus University Hospital (DK), University Hospital Carl Gustav Carus (DE), University Medical Center Groningen (NL) and Maastricht University Medical Center/Maastro Clinic (NL). The Christie NHS Foundation Trust and Swansea NHS Trust (UK) participated as validation centres.

Consensus process

All participating centres agreed on the following steps in the consensus process for the development of instructions for the delineation of target volumes in oesophageal cancer patients undergoing nCRT followed by surgery:

Step 1: Revision of published and national/institutional delineation guidelines.

Step 2: First delineation round of five cases according to the national/institutional delineation guidelines.

Step 3: Consensus meeting to discuss the results of step 1 and step 2, followed by a target volume proposal.

Step 4: Circulation of the proposed consensus with instructions for target volume delineation and atlas for feedback.

Step 5: Second delineation round of five new cases to peer review and to validate the agreed consensus delineation guidelines and atlas.

Step 6: Final consensus on the delineation guidelines depicted in an atlas.

Literature review

In step 1 of the consensus process, the MEDLINE database was searched for the terms (“Esophageal Neoplasms”[Mesh] AND “Radiotherapy”[Mesh] AND “Target Volume”[tiab] (May 2019) [17]. The detailed search strings are available in the Supplementary material (Sup. File S1). Only papers published in Dutch, English, French and German were included. All titles and abstracts were screened and studies reporting on the delineation of the target volume in the neoadjuvant setting were retained. Reviews, general overview articles, comments, congress abstracts and papers reporting on the delineation of the target volume in definitive chemoradiotherapy or on the use of imaging for delineation and treatment planning were excluded. To identify additional relevant studies, the reference lists of the retrieved studies were checked manually. Studies on the lymph node distribution after primary surgery for oesophageal cancer were beyond the scope of this project. The institutional and/or national guidelines were collected from University Hospitals Leuven, Aarhus University Hospital, University Hospital Carl Gustav Carus, University Medical Center Groningen and Maastricht University Medical Center/Maastro Clinic.

Target delineation and comparison

The web-based platform Embrace was used to share de-identified information and patient files for the delineation rounds. For the first delineation round (step 2), five patients (patient 1–5) previously treated with radiotherapy for oesophageal cancer at Aarhus University Hospital were identified. Patients were chosen to represent different clinical stages with variation in location of the primary tumour and pathological lymph node(s) (Sup. File S2). Patients for the second delineation round (step 5, patient 6–10) were chosen to match the cases in the first delineation round according to tumour location and clinical stage (Sup. File S3). In both step 2 and step 5, relevant clinical patient and tumour information was provided including a planning four-dimensional computed tomography (4D-CT) scan with 10 phases and a fluorodeoxyglucose positron emission tomography with integrated CT (FDG-PET/CT) scan in treatment position. A 3 mm slice thickness was used for the CT scan, and the 4D-CT and FDG-PET/CT scans were acquired in one session. The mid-ventilation phase of the planning 4D-CT scan was marked and used for delineation of the gross tumour volume of the primary tumour (GTVp) and pathological lymph nodes (GTVn), the clinical target volume of the primary tumour (CTVp), the nodes (CTVn) and the total volume (CTVtotal). The internal clinical target volume (iCTV) was delineated based on the planning 4D-CT to account for respiratory motion [18].

For all patients, target volumes (GTVp, GTVn, CTVtotal and iCTV) were compared between centres using MIM Software Inc., OH, US version 6.8.9. In one centre, the cases were delineated independently by two radiation oncologists. This was considered as an additional ‘centre’ for the analyses, hence resulting in delineations from six centres being available for analysis. Measures were based on the Dice similarity coefficient (DSC), maximum and mean undirected Hausdorff distances (H_{max} and H_{mean}, respectively) measured symmetrically between surfaces, the total volume and the maximum length in cranio-caudal direction [19]. The undirected Hausdorff distance was determined by finding for each point on the surface of contour A, the closest point on the surface of contour B and conversely for each point on the surface of contour B, the closest point on the surface of contour A [20]. All metrics were calculated pairwise between all possible pairs of each patient in the two delineation rounds.

All delineations were manually reviewed. Contour overlap mapping (MIM Software Inc.) was used to illustrate differences between the delineated structures using a heat map. Different colours were used for regions encompassing one to six or eight delineated volumes, leaving regions delineated by all centres colourless.

Statistics

Pairwise DSC and H_{mean} were illustrated by descriptive statistics with box plots. Differences in DSC and H_{mean} between the two delineation rounds were investigated with a Mann-Whitney U test for continuous variables using Matlab (version 2019a). As patients for the second round were selected to mimic patients in the first round, the cases were presumed to be comparable, i.e. patient one was compared to patient six, etc. Furthermore, differences in DSC and H_{mean} between the six centres participating in both rounds and the two validation centres were investigated for the second round of delineations. A p-value < 0.050 was considered statistically significant.

Results

After the annual congress of the European SocieTy of Radiotherapy and Oncology in Milan in April 2019 (ESTRO38), all participating centres agreed on the consensus process. The entire process to develop a proposal for target volume delineation and atlas took 15 months.

Step 1: Revision of published and national/institutional delineation guidelines.

Literature review

The literature was reviewed between May and July 2019. The initial search yielded 399 articles, of which 389 were excluded. Four additional relevant studies were identified from the reference lists of the retrieved studies. Literature selection results are depicted in Sup. Fig. S1.

Two articles in which two expert panels proposed delineation guidelines for the target volume in the neoadjuvant setting in oesophageal cancer were identified (Sup. Table S1) [21,22]. The first expert panel developed guidelines for the target volume for three-dimensional conformal radiotherapy (3D-CRT) or IMRT in adenocarcinomas of the gastroesophageal junction (GEJ) and the stomach based on a literature review [21]. The second expert panel focussed on the delineation of the CTV by providing consensus guidelines and an atlas for IMRT in oesophageal and GEJ cancer based on the delineation of three test cases [22]. Both expert panels proposed delineation of elective lymph node stations, depending on the location of the primary tumour.

One retrospective and three prospective studies defined the microscopic tumour extension after primary surgery for oesophageal cancer. Two of them made the following recommendations for margins from GTVp to CTVp: 3.0 cm cranial and 3.0–4.0 cm caudal along the oesophageal wall for squamous cell carcinoma and 3.0 cm cranial and 5.0 cm caudal for adenocarcinoma (Sup. Table S2) [23–26]. One prospective study reported microscopic residual tumour outside the CTV in nine among 63 patients (14%) by in situ demarcation of the CTV borders during surgery after nCRT (Sup. Table S2) [27]. Wang et al. evaluated 217 patients with a squamous cell carcinoma, and suggested a margin of 0.3–0.5 cm from GTVn to CTVn to encompass 95% of the extracapsular extension, depending on the diameter of the lymph node [28].

Six articles investigated the recurrence pattern after nCRT in oesophageal cancer patients [29–34]. Four of them described the relationship with the radiotherapy volume, three of which proposed guidelines for delineation of the target volume in the neoadjuvant setting [29–32]. Meguid et al. detected an out-of-field recurrence in 54 of 267 patients (20%). This recurrence was however defined as a failure at all sites, except the oesophagus and mediastinum, and radiotherapy details were lacking [29]. In one study, a recurrence adjacent to the planning target volume (PTV) or field edge was detected in five of 213 patients (2%), three of whom being combined with distant metastases [30]. Furthermore, three of these borderline failures occurred at the site of the celiac axis. Two patients had a solitary recurrence outside the PTV. Margins of 4.0 cm cranio-caudally and 1.5 cm radially were taken from GTV to PTV using 3D-CRT. Thoen et al. reported that 17 of 95 locoregional recurrences, occurring in 10 patients, were marginal, defined as a recurrence that received a mean dose (D_{mean}) < 34.0 Gy but a maximum dose (D_{max}) $\geq$ 34.0 Gy. This occurred simultaneously with an out-of-field (D_{mean} and D_{max} < 34.0 Gy) and/or in-field recurrence (D_{mean} $\geq$ 34 Gy). Sixty-three of 95 locoregional relapses, in 26 patients, were out-of-field. This was combined with an in-field and/or marginal recurrence in nine patients. Distant failure was the predominant mode of failure in the aforementioned studies and as a result, two studies stated that extension of the radiation target volume is unlikely to increase survival [30,31]. The fourth study reported one solitary recurrence adjacent to the PTV in 25 patients using large margins of 8.0–10.0 cm from GTV to CTV [32]. In two other articles reporting on relapse, the recurrence pattern after nCRT was compared in a matched cohort of patients with or without an extended elective nodal irradiation [33,34]. In a retrospective study of Hsu et al in 118 patients, the elective nodal volume included the supraclavicular (74%) or celiac (26%) lymph node stations depending on the location of the primary tumour [33]. The 3-year cumulative failure rate in these lymph node stations was significantly lower in the group who received an elective nodal irradiation. In a retrospective study in 222 patients with a GEJ tumour, the extended neoadjuvant radiotherapy volume included additionally the celiac and splenic (+/− porta) lymph nodes [34]. Celiac relapse was similar in patients with a locoregional or extended radiotherapy volume and no patients failed in the splenic or porta nodes [34].

National and/or institutional delineation guidelines of the participating centres

Margins of 3.0 cm (in one centre 4.0 cm) cranio-caudally along the oesophagus were applied from GTVp to CTVp. A distal margin of 2.0 cm was recommended for very distal and GEJ tumours. Radial margins of 1.0–1.5 cm were proposed. All centres delineated, either in the CTVp or CTVn, the lymph nodes stations along the CTVp, including the peri-oesophageal fat, the fatty tissue of the aortic-pulmonal fenestra, the fatty tissue of the arteria gastrica sinistra, and of the subcarinal, para/pretracheal, paracardial and supraclavicular region as far as they are within 3.0–4.0 cm cranio-caudally from the GTVp. One centre included half the aorta circumference. The margin from GTVn to CTVn varied between 0.5–1.0 cm and all centres included the involved lymph node stations in the CTVn. One centre delineated an elective nodal irradiation of the supraclavicular region for lymph node positive patients with a primary tumour above the carina. None of the centres irradiated an extended elective nodal volume, such as the celiac lymph node station in case of a distal tumour without pathological lymph nodes. The CTVtotal was corrected for anatomy if no invasion, excluding lungs, large vessels, heart and bone. An iCTV was defined in two centres as the sum of the CTVtotal in all phases of the 4D-CT scan to account for respiratory motion. In one centre, the iCTV was created using axial and longitudinal margins based on the individual movements estimated in the 4D-CT scans of the patients. The PTV-margin was centre-specific.

Step 2: First delineation round of five cases according to the national/institutional delineation guidelines.

The five cases of the first round (patient 1–5) were circulated for delineation in July 2019 (Sup. File S2). The analyses were performed in September-October 2019. The consistency in delineation between the centres was moderate with a DSC of 0.65–0.92 for GTVp (Fig. 1, left column) and 0.59–0.88 for CTVtotal (Fig. 2, left column). A range of approximately 0.2 in DSC for CTVtotal was seen for all patients except one (patient 2). For all patients, H_{mean} was low with median values ranged between 0.1–0.2 cm (maximum 0.3 cm) and 0.2–0.4 cm (maximum 0.6 cm) for GTVp and CTVtotal, respectively. The H_{max} for CTVtotal was 5.0 cm in patient 5, while the median values ranged from 2.0-3.1 cm. Consistency between centres in delineation of GTVn varied between the patient cases; in one case, there was a large difference in the number of lymph nodes delineated. Some of the inconsistencies may be explained by the limited clinical information provided, e.g. no information on the location of malignant lymph nodes and no detailed information on the diagnostic scans. Generating the CTV's was done according to local guidelines as described above. The predominant difference in delineation of the CTVtotal was determined

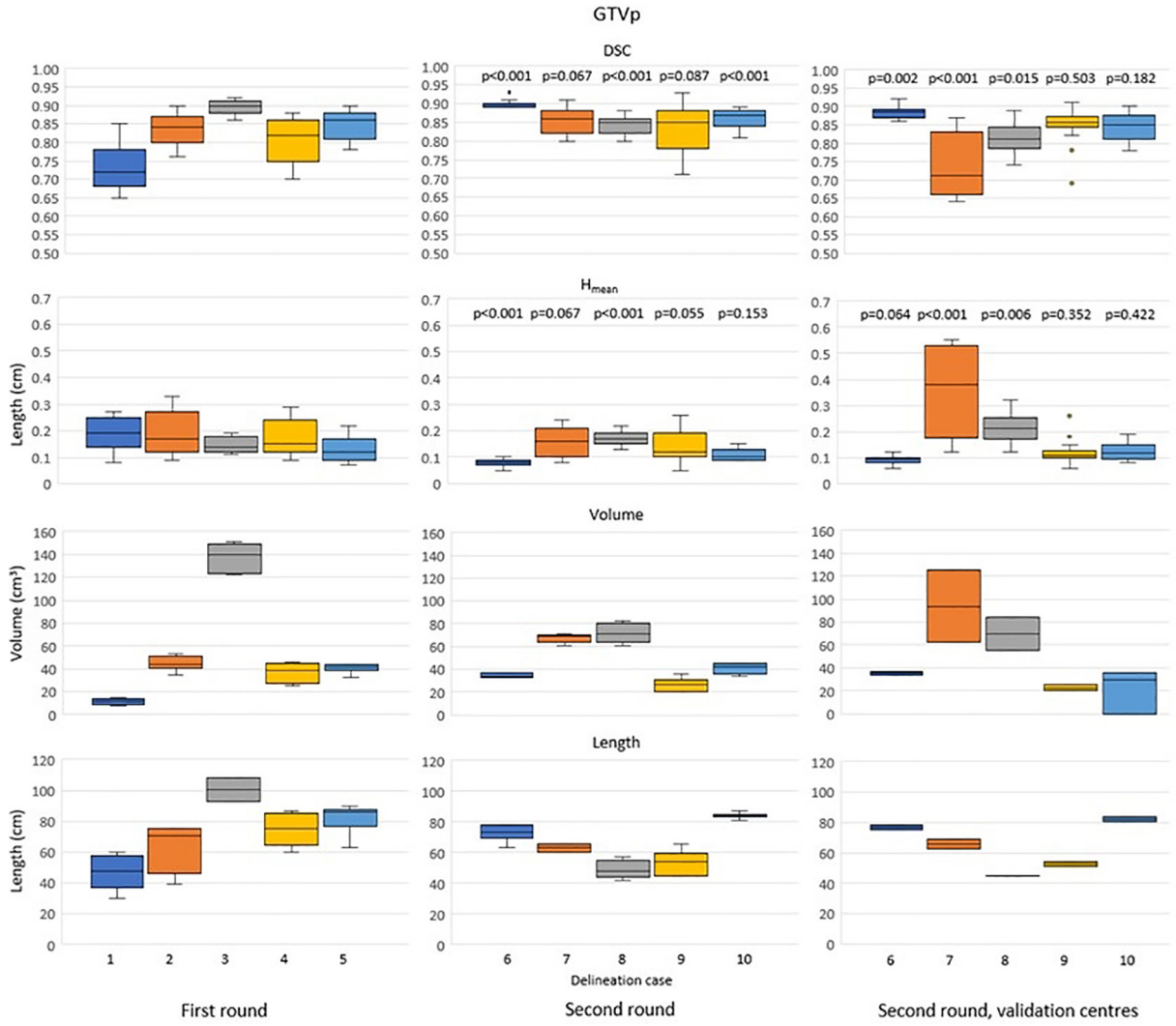

Fig. 1. Comparison of selected metrics for GTVp for the first (patient 1–5) and second (patient 6–10) delineation round. The pairwise Dice similarity coefficient (DSC) and mean Hausdorff distances (H_{mean}) are presented for the first (left; patient 1–5) and second (centre, patient 6–10) delineation round for the six centres participating in both rounds. The right column shows the pairwise DSC and H_{mean} between the two validation centres and the six centres participating in both rounds. Additionally, the volumes and cranio-caudal length of the gross tumour volume of the primary tumour (GTVp) are shown for the six centres (left and centre) and the two validation centres (right). Box plot: median (horizontal line), first and third interquartile ranges (box), minimum/maximum (whiskers), and outliers (o). The *p*-values of a Mann-Whitney U test are shown for DSC and H_{mean} for the comparison of the two delineation rounds (centre) and the comparison between the six centres participating in both rounds and the two validation centres (right). A *p*-value < 0.050 was considered statistically significant. DSC = Dice similarity coefficient; H_{mean} = mean Hausdorff distances; GTVp = gross tumour volume of primary tumour.

by the definition of the lymph node stations along the CTVp (Fig. 3). All centres were asked to create an iCTV to account for respiratory motion. One centre defined the iCTV with geometric margins yielding a considerable larger cranio-caudal expansion from CTVtotal to iCTV (Fig. 4). In one centre, the expansion from CTVtotal to iCTV was considerable smaller than in other centres.

Step 3: Consensus meeting to discuss the results of step 1 and step 2, followed by a target volume proposal.

In November 2019, the participating centres had a consensus meeting in Leuven discussing the literature review and results of the first delineation round. A thoracic surgeon specialised in oesophageal surgery attended this meeting.

- All centres agreed to apply margins of 3.0 cm cranio-caudally from the GTVp to the CTVp, and 2.0 cm caudally in case of a distal oesophageal or GEJ tumour. The lymph node stations along these 3.0 cm cranio-caudally should be included in the CTVp. The volume was defined as the peri-oesophageal lymph nodes, including the vena azygos, the aortic-pulmonal fenestra, the fatty tissue of the arteria gastrica sinistra, of the subcarinal, para/pretracheal, paracardial and supraclavicular region as far as they are within 3.0 cm cranio-caudally from the GTVp.
- An extensive elective nodal volume should be omitted, and only the involved lymph node stations should be additionally irradiated.
- All CTV's, except the iCTV, should be corrected for anatomy.
- Cervical oesophageal cancers are not included in this target volume delineation proposal.

After the meeting a first draft of instructions for target volume delineation and an atlas were generated.

Step 4: Circulation of the proposed consensus with instructions for target volume delineation and atlas for feedback.

In February 2020, the proposed instructions for delineation of target volumes and the atlas were circulated between the participating centres and a limited number of modifications were made.

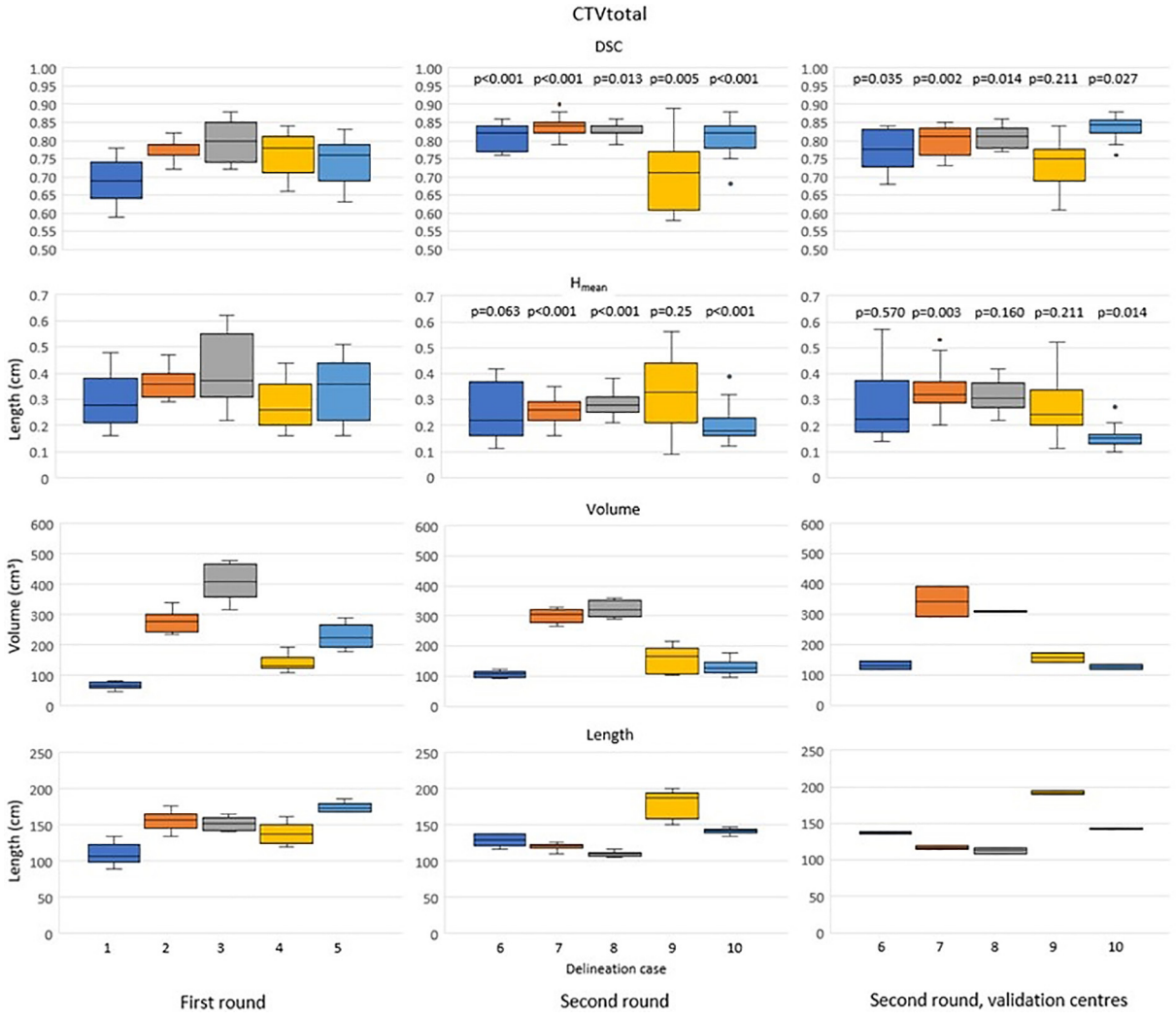

Fig. 2. Comparison of selected metrics for CTVtotal for the first (patient 1–5) and second (patient 6–10) delineation round. The pairwise Dice similarity coefficient (DSC) and mean Hausdorff distances (H_{mean}) are presented for the first (left, patient 1–5) and second (centre, patient 6–10)) delineation round for the six centres participating in both rounds. The right column shows the pairwise DSC and H_{mean} between the two validation centres and the six centres participating in both rounds. Additionally, the volumes and cranio-caudal length of the CTVtotal are shown for the six centres (left and centre) and the two validation centres (right). Box plot: median (horizontal line), first and third interquartile ranges (box), minimum/maximum (whiskers), and outliers (o). The *p*-values of a Mann-Whitney U test are shown for DSC and H_{mean} for the comparison of the two delineation rounds (centre) and the comparison between the six centres participating in both rounds and the two validation centres (right). A *p*-value < 0.050 was considered statistically significant. DSC = Dice similarity coefficient; Hmean = mean Hausdorff distances; CTVtotal = total clinical target volume.

Firstly, the delineation of the lymph node stations along the CTVp was included in the CTVn. Secondly, the decision was left up to the treating physician whether to expand the CTVtotal or to irradiate two separate volumes if the distance of a gap between CTV's is more than 3.0 cm.

Step 5: Second delineation round of five new cases to peer review and to validate the agreed consensus delineation guidelines and atlas.

In March 2020, the five new cases of the second delineation (patient 6–10) round were circulated (Sup. File S3).

The DSC and H_{mean} for GTVp and CTVtotal for the second delineation round for the six centres participating in both rounds are shown in Fig. 1 and Fig. 2 (centre column). For patient 6, 7, 8 and 10, the DSC was significantly larger for CTVtotal than in the first delineation run. Ranges of approximately 0.1 in DSC were seen for all patients, except for patient 9 showing wider range and significantly lower DSC in the second round. H_{mean} values were in the range of 0.1–0.2 cm (maximum 0.26 cm) and 0.2–0.3 cm (maximum 0.6 cm) for GTVp and CTVtotal, respectively. For patient 9, H_{mean} for CTVtotal was larger in the second round. In this patient, the primary tumour was located in the distal oesophagus whereas one malignant lymph node was located in station 2R, resulting in a more than 3.0 cm distance between the CTVp and the CTVn. Two centres chose to irradiate two separate volumes (Fig. 3). The range in volume and length of the CTVtotal was smaller for all six centres, except for patient 9.

The DSC and H_{mean} for GTVp and CTVtotal between the two validation centres and the six centres participating in both rounds are shown in Fig. 1 and Fig. 2 (right column). Significantly lower DSC was obtained for CTVtotal for the two validation centres in patient 6, 7 and 8. No difference was seen for patient 9 and significantly better DSC was seen in patient 10. H_{mean} for CTVtotal was not significantly different in patients 6, 8 and 9. It was significantly larger in patient 7 and smaller in patient 10.

In general, delineations in the second round were much more consistent between centres, with the highest homogeneity between the centres participating in the consensus meeting compared to the validation centres. Areas of discrepancies in the second round were the anterior border of CTVn (though minor in this round) and the above described voluntary expansion of CTVtotal to include gaps (Fig. 3). Delineation of GTVn was more consis-

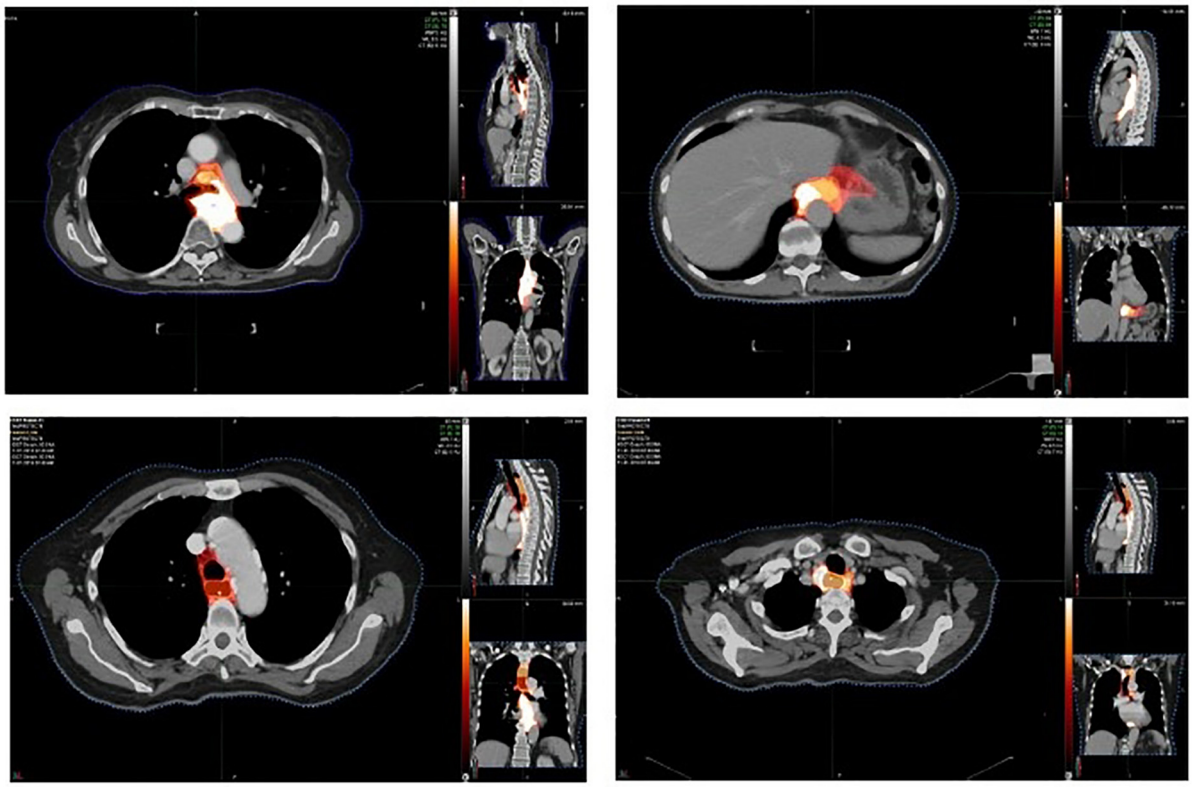

Fig. 3. Delineation examples. The agreement in the delineation between centres is showed for patient 4 (upper left), patient 6 (upper right) and patient 9 (bottom left and right). Areas marked with white/no colour shows an agreement between all six (patient 4) or eight (patient 6 and patient 9) centres and areas marked with dark red shows an agreement with only one centre.

tent which may be explained by a more thorough description of the location of malignant lymph nodes. iCTV was created according to the proposed guidelines with less variability between the centres (larger DSC and p-value < 0.050 for all patients except for patient 9) (Fig. 4).

Step 6: Final consensus on the delineation guidelines depicted in an atlas.

After the second delineation round, a description of the lymph node stations was included into the proposed instructions for target volume delineation [35].

A consensus was obtained for the delineation of the GTVp, GTVn, CTVp, CTVn, CTVtotal and iCTV in oesophageal cancer patients undergoing nCRT. The proposed instructions for delineation of the target volumes was defined as the following (delineation atlas in Fig. 5, Fig. 6 and Sup. File S4):

- **GTVp** includes the primary tumour (with the oesophageal wall) as seen on the planning (FDG-PET/)CT scan and includes all available information (e.g. endoscopy, echo-endoscopy (EUS), diagnostic (FDG-PET/)CT, magnetic resonance imaging (MRI), fiducial markers). The GTVp includes the entire oesophageal wall but does not include the peri-oesophageal fat. If fiducial markers are placed at the tumour borders, they should be included in the GTVp.
- **GTVn** includes the involved lymph nodes defined as pathological any time before the radiation therapy. Lymph nodes that appear as new on the planning (FDG-PET/)CT compared to the diagnostic FDG-PET/CT, suspected for malignant lymph nodes, have to be included in GTVn. A fine-needle aspiration cytology (FNAC) is recommended in case of doubt and when it has an impact on the delineation of the target volume. Delineation is done on the planning (FDG-PET/)CT and includes all available information (e.g. endoscopy, EUS, endobronchial ultrasound (EBUS), diagnostic (FDG-PET/)CT, biopsy, MRI, ultrasound).
- **CTVp** includes the GTVp with an expansion of 1.0 cm radially and 3.0 cm cranio-caudally along the oesophageal wall. For tumours in the lower oesophagus and GEJ, the CTVp is restricted to 2.0 cm distal to the tumour. The CTVp is corrected for anatomy (muscles, bones, large vessels and OARs) if no invasion.
- **CTVn** includes the GTVn with an expansion of 1.0 cm in all directions and the lymph node stations at this level. Additionally, it includes the lymph nodes stations along the CTVp according to the classification of Hagens et al. [35], including the para-oesophageal lymph nodes, the vena azygos, the aortic-pulmonal fenestra, the fatty tissue of the arteria gastrica sinistra, of the subcarinal, para/pretracheal, paracardial and supraclavicular region as far as they are within 3.0 cm cranio-caudally from the GTVp. The CTVn is corrected for anatomy (muscles, bones, large vessels and OARs) if no invasion.
- **CTVtotal** is the sum of CTVp and CTVn. The CTVtotal is expanded to include potential gaps between the CTV's. These potential gaps should always include the oesophagus and the lymph nodes station at that level. Depending on the location of the gaps, the para-oesophageal lymph nodes, the aortic-pulmonal fenestra, the fatty tissue of the arteria gastrica sinistra, and the subcarinal, para/pretracheal, paracardial and supraclavicular region should be delineated along the CTVtotal. If the distance of the gap is more than 3.0 cm, the decision to expand the CTVtotal or to irradiate two separate volumes is up to the treating physician.
- **iCTV** is the sum of the CTVtotal in all phases of the 4D-CT scan to account for respiratory motion. The iCTVtotal can include muscles, large vessels and OARs.

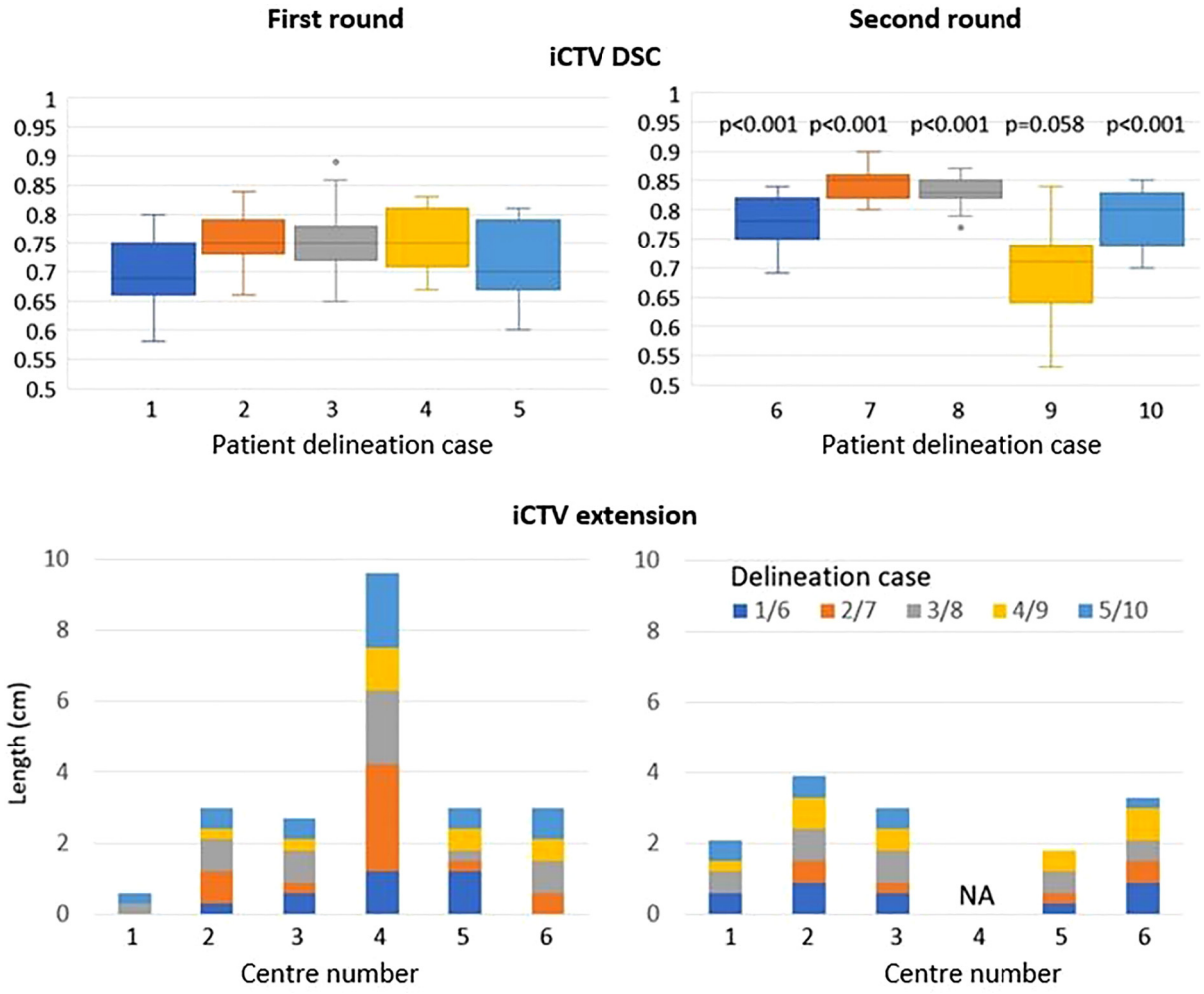

Fig. 4. The difference between centres in the delineation of the iCTV for the patients in the first (patient 1–5) and second (patient 6–10) delineation round. Top: The pairwise Dice similarity coefficient (DSC) for the iCTV is presented for the first (patient 1–5) and second (patient 6–10) delineation round for the six centres participating in both rounds. The *p*-values of a Mann-Whitney U test are shown. A *p*-value < 0.050 was considered statistically significant. Bottom: Stacked bar charts of the cranio-caudal expansion in length from CTVtotal to iCTV for the patients in first (patient 1–5) and second (patient 6–10) delineation round are presented for the six centres participating in both delineation rounds. One centre (centre 4) did not expand in the cranio-caudal direction in the second delineation round. However, the expansion in this direction for other centres is also limited (one or two slices). All centres expanded in the lateral and anterior-posterior direction (not shown). CTVtotal = total clinical target volume; iCTV = internal clinical target volume; DSC = Dice similarity coefficient; *p* = *p*-value.

Discussion

The use of more conformal radiotherapy techniques, such as IMRT and proton therapy, urges the need to standardise the definition of the radiation target volume in oesophageal cancer. In order to compare treatment outcomes between various radiotherapy techniques across different centres, uniform prospective patient cohorts are required. Therefore, we proposed instructions for target volume delineation and an atlas for oesophageal cancer patients treated with nCRT followed by surgery.

After a literature search, we found two articles with consensus delineation guidelines, proposed by two expert panels [21,22]. The first panel recommended guidelines based on a literature review, whereas the second panel used three test cases as evidence acquisition. We noticed, however, a persistent variability in the delineation of the target volume across European centres. Our consensus process was based on both an extensive literature review and on the delineation of 10 test cases in two delineation rounds by several European centres. The delineations of the second round were much more consistent with a similar variability reported previously for other indications [36–39]. However, there was more variability in the delineation among the two validation centres, both UK centres, that only participated in the second round and did not attend the consensus meeting. Although, their performance was still better than the delineations of the centres in first round without the proposed consensus guidelines, this underlines the need for both the development of guidelines and training in use of these guidelines [40]. Furthermore, a strict quality assurance protocol for target volume delineation during clinical trials is required [41]. After the second delineation round, our instructions for delineation were further fine-tuned. We specified more clearly the delineation of the lymph node stations [35]. Additionally, it was decided that the lymph node stations along the CTVp could be included either in the CTVp, as in the first delineation round, or in the CTVn, as in the second delineation round. The CTVp and the CTVn is combined into a CTVtotal. From this the iCTV is propagated, being the final volume to irradiate.

Our suggestion of a 3.0 cm margin cranio-caudally along the oesophageal wall from GTVp to CTVp to encompass the microscopic tumour extension, was in line with the previous consensus guidelines and the existing literature [22,25,26]. Smaller margins seem not appropriate, given the devastating impact on disease free and overall survival by the detection of microscopic residual tumour outside the CTV [27]. For tumours close to or involving

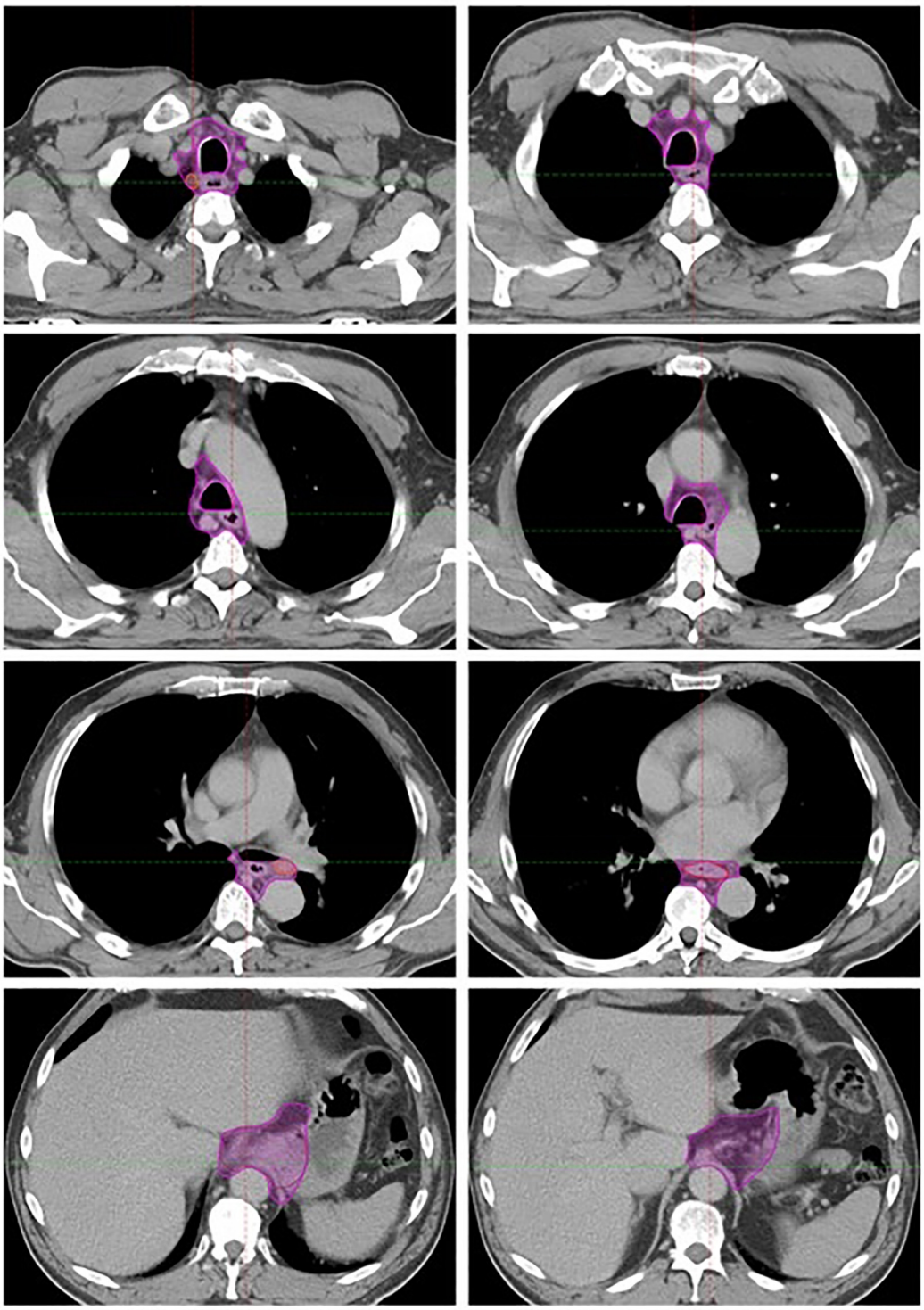

Fig. 5. Delineation of a patient with a distal tumour and two involved peri-oesophageal lymph nodes. The CTVtotal (*purple*) is the sum of CTVp (*brown*) and CTVn (*green*). GTVp (*red*) is expanded 3.0 cm cranially, 2.0 cm caudally (distal tumour) and 1.0 cm radially along the oesophageal wall to the CTVp. The CTVn includes the lymph node stations at the level of and minimally 1.0 cm cranio-caudally of the GTVn (*orange*). Additionally, the CTVn includes lymph node stations along the CTVp, including the para-oesophageal lymph nodes, the para/pretracheal region, the vena azygos, the aortic-pulmonal fenestra, the subcarinal and paracardial region and the fatty tissue of the arteria gastrica sinistra. The total gastro-hepatic ligament should not be included anteriorly in the CTVn. In this patient, the CTVtotal could be expanded to include gaps between the CTV's (>3.0 cm). A more detailed description of the target volumes is available in Sup. File S4. GTVp/n = gross tumour volume of primary tumour or pathological lymph nodes; CTVp/n = clinical target volume of primary tumour or lymph nodes; CTVtotal = total clinical target volume.

the GEJ, a distal margin of 2.0 cm along the oesophageal or gastric mucosa was recommended in order to avoid the irradiation of large parts of the stomach, except when a significant tumoural infiltration in the stomach is present.

We recommended to only delineate the involved lymph node stations and these along the CTVp. This is a balance between the extensive elective nodal irradiation that was used in the past and an involved-field irradiation with inclusion of only the involved

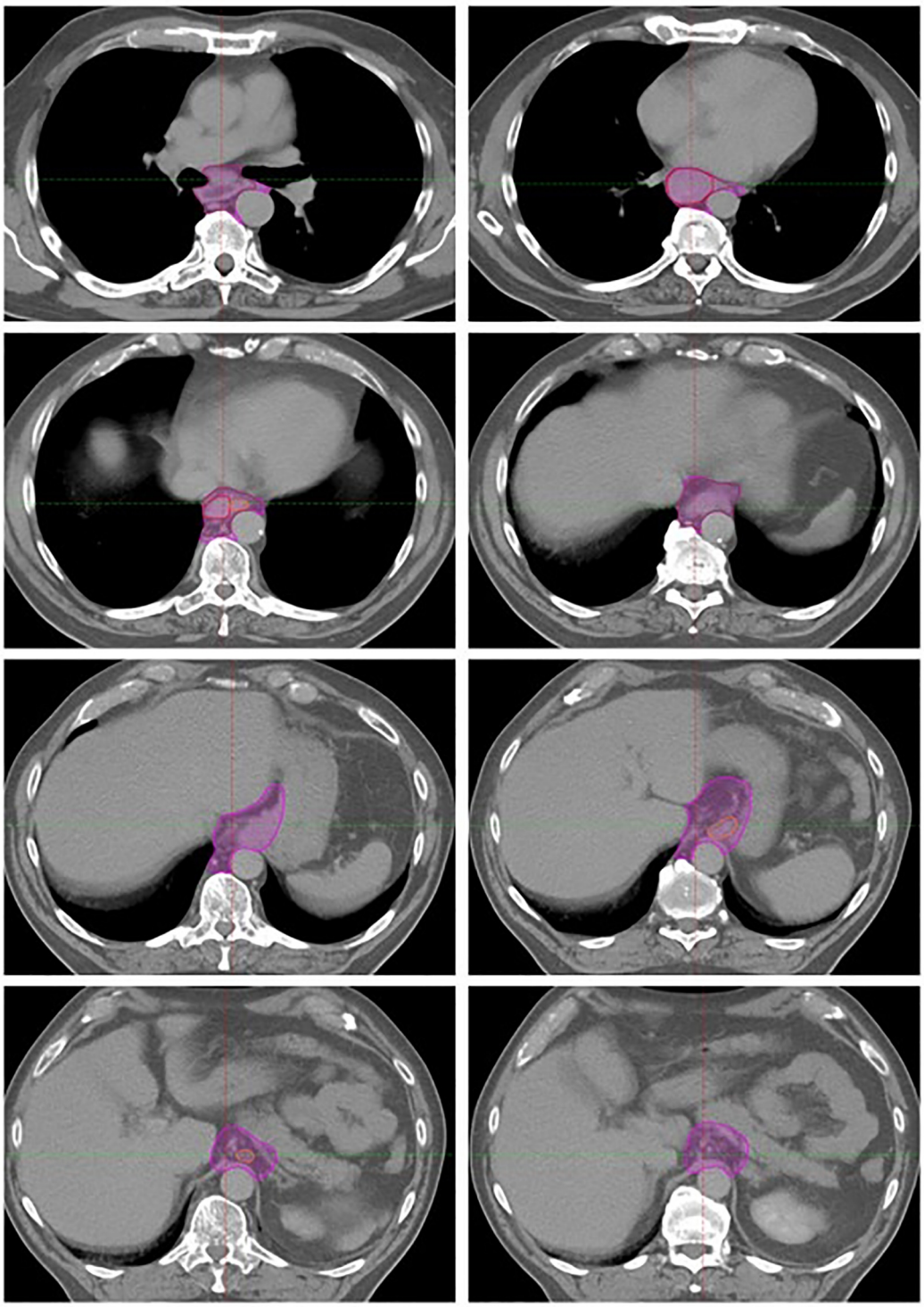

Fig. 6. Delineation of a patient with a distal tumour with a peri-tumoural and abdominal involved lymph node. The CTVtotal (*purple*) is the sum of CTVp (*brown*) and CTVn (*green*). GTVp (*red*) is expanded 3.0 cm cranially, 2.0 cm caudally (distal tumour) and 1.0 cm radially along the oesophageal wall to the CTVp. The CTVn includes the lymph node stations at the level of and minimally 1.0 cm cranio-caudally of the GTVn (*orange*). Additionally, the CTVn includes lymph node stations along the CTVp, including the para-oesophageal lymph nodes, the vena azygos, the aortic-pulmonal fenestra, the subcarinal and paracardial region and the fatty tissue of the arteria gastrica sinistra. The total gastro-hepatic ligament should not be included anteriorly in the CTVn. A more detailed description of the target volumes is available in Sup. File S4. GTVp/n = gross tumour volume of primary tumour or pathological lymph nodes; CTVp/n = clinical target volume of primary tumour or lymph nodes; CTVtotal = total clinical target volume.

lymph node stations. Most data involving a comparison between both approaches were obtained from retrospective Asian studies in patients with squamous cell carcinoma, mostly treated with definitive chemoradiation [42,43]. Moreover, as shown in our literature review, an elective or involved nodal irradiation was not uniformly defined [33,34]. Additionally, radial margins of 1.0–2.0 cm from GTVp to CTVp includes the peri-oesophageal lymph nodes and probably (partially) other lymph node stations. The use of more advanced radiotherapy techniques can however lead to reduction of the historical incidental irradiation of lymph node sta-

tions. So it is not obvious to compare the results of different studies over time. Based on the institutional guidelines of the participating centres and after discussing this topic at the consensus meeting, we agreed to only include the involved lymph node stations and stations along the CTVp. This is in contrast to the consensus guidelines of Wu et al., where the celiac axis or supraclavicular lymph node stations were electively included for distal or proximal tumours respectively [22].

There was a disagreement on the expansion of the CTVtotal in case of a gap of more than 3.0 cm between the CTV's. We left this decision up to the treating physician, as this will affect only few patients and reliable data in the literature are missing.

In the first delineation round, one centre had a larger expansion from CTVtotal to iCTV based on their institutional guidelines. This was resolved in the second delineation round by providing a description of the generation of the iCTV in the guidelines.

Limitations of the study include that these proposed instructions for target volume delineation focussed on patients with an oesophageal or GEJ tumour irradiated in the neoadjuvant setting. We did not discuss the delineation of the target volume in patients treated with definitive chemoradiation, nor in patients with a tumour of the cervical oesophagus or stomach. For these patients, different delineation guidelines are needed. Moreover, we acknowledge that these instructions and atlas are not applicable to every individual patient. We provide a comprehensive atlas with patient examples, which is complementary to the clinical judgement of the treating physician. Lastly, we did not elaborate on the radiation prescription dose, on radiotherapy treatment planning and treatment delivery. These topics will be discussed in a separate protocol in the PROTECT trial consortium.

In conclusion, we defined a proposal for the delineation of the radiation target volume in the neoadjuvant setting for oesophageal cancer, including an atlas. These will be used in the PROTECT trial. Also, outside the scope of this trial, the guidelines and atlas can lead to uniformly delineated cohorts of patients and will have an impact on the quality of radiation therapy in a broader perspective. To further refine and update delineation guidelines, prospective data on the pattern of failure in oesophageal cancer patients treated with nCRT are needed. This must be based on uniform patient cohorts treated with more conformal radiotherapy techniques.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.11.032.

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