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Original Article

ESTRO ACROP guidelines for the delineation of lymph nodal areas in upper gastrointestinal malignancies

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ABSTRACT

The European SocieTy for Radiation and Oncology -Advisory Committee on Radiation Oncology Practice (ESTRO-ACROP) endorsed a project to provide guidelines (GL) for the identification and delineation of clinically negative lymph-nodal stations (LNs) involved in upper gastrointestinal clinical scenarios. The presented GL is focused on preoperative (or definitive) setting. The project aim is to improve the consistency of clinical target volume (CTV) delineation by providing: a description of the anatomical boundaries of the LNs; a radiological computed tomography-based atlas depicting the LNs areas; a free, web-based, interactive example case for independent training of radiation oncologists on LNs delineation according to the presented GL, by both qualitative and quantitative analysis (through the FALCON EduCase platform).

This project was carried out with the intention to facilitate and improve uniformity of future upper gastrointestinal guidelines on nodal CTV delineation. We report methodology and results from the collaboration of a working group panel selected by the ESTRO-ACROP.

Clinical target volume (CTV) delineation is one of the cornerstones of radiotherapy. Unfortunately, although radiation oncologists (ROs) are aware of the importance of that step, inter-observer variation in delineation has been reported in most tumor sites and has been identified as an important source of geometric uncertainty [1–4]. Some analyses reported consequent systematic errors affected by standard deviations up to 1 cm [5]. Like a double-edged blade that issue is complicated both by the definition of which lymph-nodal stations (LNs) should be included in the CTV for each clinical presentation, and by the risk of inconsistent delineation of a certain LNs due to different interpretation of their anatomical boundaries. Inter-observer delineation variability

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has been extensively described in upper gastrointestinal tract cancers (UGItc) [6,7], along with the related issue for quality assurance in clinical trials [8]. Moreover, the clinical impact of delineation inhomogeneity is barely approached in the literature and such uncertainty remains an open issues [9].

The accurate target delineation in UGItc presents specific issues due to large anatomical variability of the main vessels along which the LNs lie, with clear consequences for planning treatment volume (PTV) definition [10]. Guidelines (GL) describing which LNs and volumes are to be included into the CTV for UGItc, have been published [11–18]. However, few papers addressed the issue of what anatomical boundaries should be adopted to adequately delineate each LNs in UGItc [13,19–27]. Moreover, among the currently available GL, a non-uniform approach in boundary description, illustration, and representation in radiological atlases have been applied.

Therefore, the European SocieTy for Radiation and Oncology - Advisory Committee on Radiation Oncology Practice (ESTRO-ACROP) endorsed a project to provide GL for the identification and delineation of LNs involved in UGItc. This GL is focused on preoperative (or definitive) setting. The project aims to improve the consistency of CTV delineation by providing the following tools: (1) a LNs anatomical boundary description, (2) a radiological computed tomography (CT)-based atlas showing LNs and (3) a free web-based interactive example case for independent training of ROs on LNs delineation according to the presented GL. In addition to the delineation GL and the table of boundaries for LNs, this article provides the link to the online CT-based clinical case delineated and peer reviewed by the consensus panel. This project was undertaken to facilitate and improve uniformity of future GLs on nodal CTV delineation in upper gastrointestinal tumors.

Materials and methods

Participants

A working group (WG) of 19 experts was designated by the ACROP committee and collaborated on the project. Among them were seven ROs (VV, FC, TB, FR, BDB, OM, EG, MV), two radiologists (AR, RM), and six surgeons skilled in abdominal, hepatic, and thoracic surgery (WA, SA, FA, FG, SM, VP) who collectively developed the GL. Three additional ROs revised the process, not being previously involved in its development (AGM, CB, KH). Surgeons and radiologists expert in UGItc were involved in the discussion of the anatomical boundaries and in the validation process of the LNs delineation on a CT-based clinical case.

Consensus process

At the initial meeting the project supervisors (VV and MV) agreed with the other WG members of the project on the roadmap towards establishing the GL. The following steps were planned:

Step 1: collection of available GLs on LNs description and/or delineation by a literature search on the PubMed library. The search strategy included the following terms with various combinations: "radiotherapy"; "CTV"; "delineation"; "contouring"; "lymph-nodes"; "nodal areas"; "gastrointestinal"; "stomach"; "gastric"; "pancreas"; "liver"; "biliary tract"; "esophagus"; "preoperative"; the search was manually refined and included also other papers suggested by the WG participants. Papers were excluded if they provided indication on CTV delineation for UGItc without information on LNs identification or delineation by anatomical boundaries or by either a pictorial or a radiological atlas [15]. The classification proposed by the Japanese Gastric Cancer Association (JGCA) [23] was selected as the reference one.

Step 2: organization of data extracted from the selected GLs, for each LNs, in a synopsis. A selection of anatomical tables to focus the discussion of the WG was also carried out.

Step 3: selection of a non-oncological subject diagnostic contrast-enhanced CT scan (by the 2 radiologists and one RO) for LNs delineation. The educational web-based multifunctional platform for delineation endorsed by ESTRO (FALCON EduCase) was used to support the consensus process and to facilitate the validation process by either on-line or live meeting discussions.

Step 4: delineation on the selected CT scan by ROs: prior to the first WG live meeting, 15 relevant slices were selected for preliminary individual delineation of all LN areas represented on each selected slice. The ROs were requested to draw delineations based on their personal experience and on the synopsis summarizing literature evidence (see Step 2).

Step 5: review of the inter-observer qualitative variation by the WG members (including radiologists and surgeons); this step enabled the boundaries definition for each LNs. Moreover, an "author's master delineation" was separately drawn and validated by the whole WG. First of all each LNs was discussed separately. Thereafter, a double-checked was performed by topographically displaying all LNs of each CT slice to detect contouring inconsistencies.

Step 6: peer review of the consensus to draft a first version of LNs boundaries.

Step 7: second round of delineation based on the first version of LNs boundaries definition, with repeated one-by-one LNs discussion.

Step 8: meeting(s) to validate the final consensus guidelines.

Step 9: completion of the GL with boundary description per individual LNs and of the interactive delineation atlas to be published on the FALCON EduCase platform.

Results

Timeframe

At the "ESTRO 36" Conference (Vienna, 2017) the concept of the project was initially discussed. After resources evaluation and WG involvement, at the "ESTRO 37" Conference (Barcelona, 2018) the initial meeting was held and the roadmap was defined and agreed among participants. Steps 1 to 4 were developed. After the 1st round of individual delineation of the clinical case using the FALCON EduCase platform, the first live meeting of the WG, including all radiologists and surgeons, was held in Rome on September 2018 (Step 5). After that, on-line meetings were held to discuss arisen questions and issues and to provide the WG with the draft version of LNs boundaries description (Step 6). Subsequently, a second individual run of delineations was performed by the ROs on the same CT scan by using the draft version of the LNs boundaries description (Step 7).

At the "ESTRO 38" Conference (Milan, 2019) a meeting was organized to discuss the ongoing project progression and the remaining open questions. In order to complete Step 8, a final live meeting was organized in Rome, on September 2019, again involving the whole WG (including all radiologists and surgeons), to provide a final version of LNs boundary descriptions and an "author's master delineation" of all LNs. Step 9 was completed by an online final approval of the documents after individual double-check by ROs, one radiologist (AR), and one surgeon (WA). Finally, the core documents (i.e., the table reporting boundary descriptions for LNs and the online CT-based clinical case delineated on each slice per each LNs) along with the draft of this manuscript were separately evaluated by the WG reviewing committee.

LNs boundaries

Table 1 reports the anatomic boundaries of each LNs. The LNs were categorized, based on the JGCA classification, [23] as follows: 1–14; 16a1; 16a2; 16b1; 16b2; 17–20; 110; 111; 112. It should be noted that the LNs 15 was not included as its delineation was not considered clinically relevant by the WG from a ROs perspective in any clinical indication/setting. LNs 11p and 11d are combined and reported as a single one (i.e.: 11p + d); nevertheless, the notes along the table report how to discriminate them. LNs 12 is defined as a single site (i.e.: combination of LNs 12a + b + p) being considered clinically not relevant by the WG a separate description of the single sub-sites CTVs.. If needed, the FALCON EduCase platform provides an option to depict the sub-site delineation of LNs 12a, 12b, and 12p in the CT- based clinical case.

For each LNs, the boundaries indicating the "Upper Border", "Inferior Border", "Anterior Border", "Posterior Border", "Right Lateral Border" and "Left Lateral Border" are reported.

Boundary's descriptions are stated per single nodal station and they are drawn on the patient in the supine position. Left and Right border refer to the Left/Right of the patients on the CT Scan (in supine position). When needed, additional notes per each LNs are also reported.

Due to the expansion step from vessels, some nodal areas overlap with each other, and that should be taken into account by ROs while delineating, although the final CTV delineation is not affected due to the merging of one structure with the possibly overlapping one.

CT-based clinical case delineation (FALCON EduCase platform)

The delineation of the CT- based clinical case validated by the whole WG (including ROs, radiologists and surgeons) is available on FALCON EduCase online platform at the following link (http://estro.educase.com/cases/index.php?-

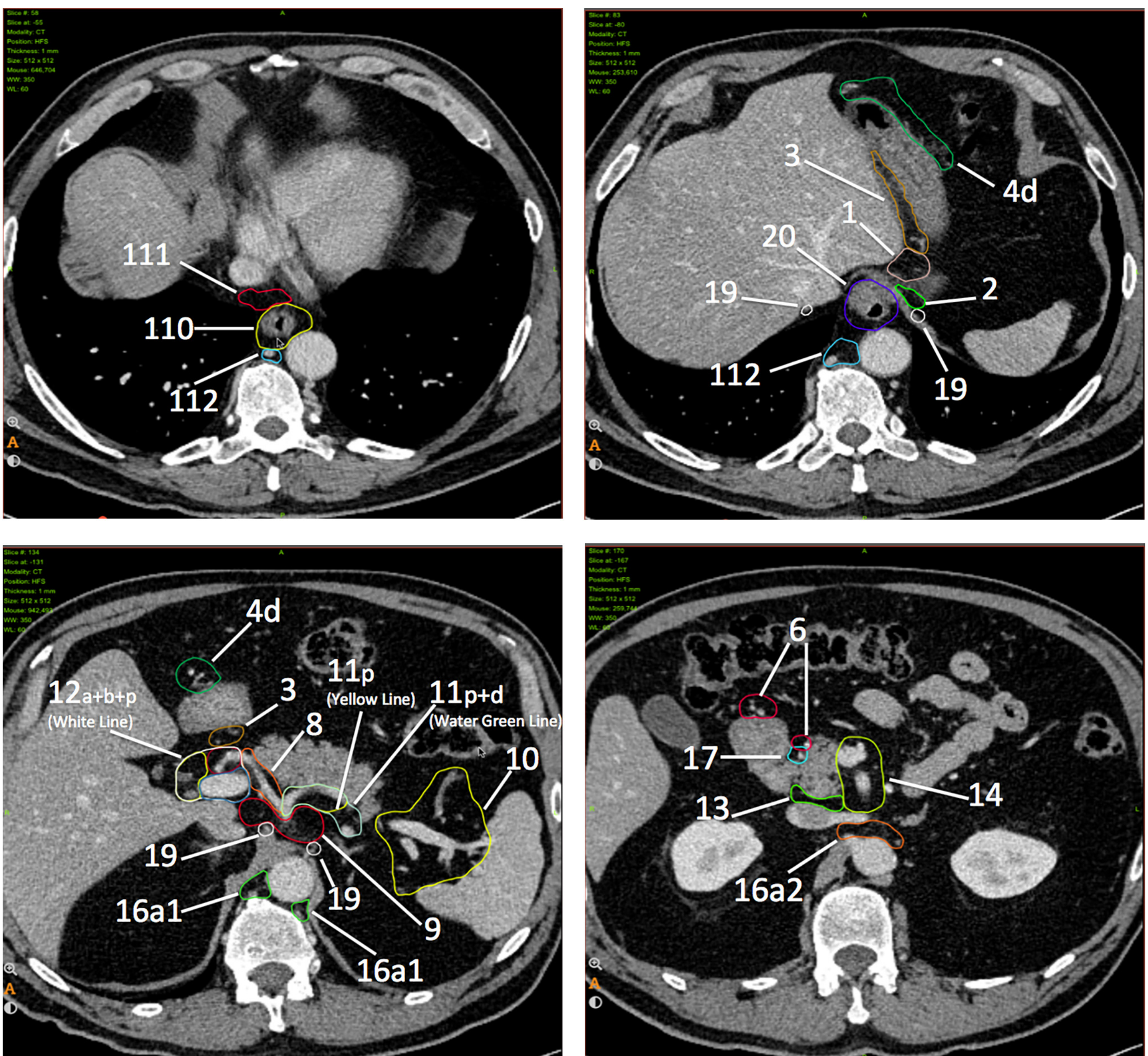

Fig. 1. Example of atlas of LNs delineation validated by the WG.

case=32909ac655c190aa5a8a81b757572dc3#!/). As previously mentioned, a contrast-enhanced CT scan was used and considered the reference imaging to delineate CTV by the WG. Fig. 1 (1a-q) shows the detailed CT-based Atlas. As example, Fig. 1a, 1c, 1h and 1n are displayed, while the whole figure set is available in the Supplementary Material.

Through the ESTRO Library, the whole CT scan is freely available and all LNs are delineated on each slice. Each LNs can be either separately displayed or along with multiple others at the same time. Multi-planar imaging reconstructions are also possible to check topographic anatomical correlations between LNs and anatomical structures (Fig. 2).

Moreover, the FALCON EduCase online platform provides the ROs with an interactive delineation opportunity. The CT-based clinical case (once accessed through the same link), enables individual delineation of any LNs. Furthermore, besides the individual delineation of each LNs, the reference delineation (validated by the WG) can be displayed to check qualitative differences. Fig. 3 shows an example of an individual delineation compared to the validated one. Finally, a quantitative evaluation of the RO's delineation homogeneity compared to the validated one is possible through the EduCause STAPLE™ algorithm. A guide to the tools and basic use of FALCON EduCase is available at (https://estro.educase.com/index.php/documents/instruction-manuals/397-educase-user-guide-html5-v01/file).

Discussion

The ESTRO-ACROP committee endorsed this project to provide GLs supporting ROs in clinically negative LNs identification and to ensure homogeneity of the delineation in UGItc, through the collaboration of a selected WG selected by ESTRO-ACROP. Target delineation inhomogeneity represents a well-known issue for ROs, compromising the efficacy of radiotherapy and influencing both the reproducibility of clinical trials and their interpretation [5,8,9]. This issue is particularly relevant in UGItc [28–31]. Differences in CTV reproducibility are mainly based on: (1) use of different imaging modalities (e.g.: CT, MRI, CT-PET) [7,32], (2) variable definition of LNs to be included into the CTV for each clinical presentation of the different UGItc primary tumors; (3) potential inter-observer variation of LNs topographic delineation.

Some GLs help ROs to standardize the selection of LNs to be included in the CTV [13,15,18]. Other GLs also show how to properly delineate each LNs of interest in UGItc [19–22]. The available GL of the latter type often show a wide variation in their descriptive approach. Considering the ones selected for our project [13,19–27], some reported only general information about boundaries definition [13,23–27] for each LNs instead of providing detailed descriptions (although referring to other sources of information), as was done in other GLs [19–22]. Some GLs described the LNs providing anatomical information [19–24]. Moreover, most GLs used pictorial (non-radiological) images, except for only 3 missing this type of information [19,22,26]. All but two studies also used some radiological imaging to show the LNs topographic distribution [23,24]. Only three GLs provided both boundaries description and pictorial-radiological images [20,21,24]. However, among them, the paper of Lengelè et al. [24] did not refer to the JGCA classification. Moreover, Huang's et al. atlas [20] mostly deal with thoracic lymph nodal delineation, thus the available information on UGItc are limited to LNs 110, 111, and 112.

At the best of our knowledge, none of the available GLs on LNs delineation in UGItc provides an interactive atlas to train the RO's delineation skills. The LNs delineation GL presented in this manuscript have been developed on the basis of a progressive work planned with a step-by-step workflow, similarly to a previously published experience [5]. First, investigating the data sources available in literature (through literature search) and most commonly used by ROs in the WG for their routine clinical activity; then, analyzing their descriptive approach, potential limits and extracting the most useful information from each GL (through a synoptically overview). This peer-review process within the WG involved the ROs in the first literature sources selection and subsequently included radiologist and surgeons to reach a consensus on the final version of the GL.

The final structure provides:

- a table of content reporting the boundaries for each LNs;
- a summary atlas with multiple representative images extracted by the CT-based clinical case (along with this manuscript);
- an online full CT-based clinical case with delineation of all LNs in each slice;
- an online interactive case on the FALCON EduCase platform enabling the ROs to individually delineate the LNs of interest and check their own contouring differences by the "author's master structures" validated by the WG, through both qualitative and quantitative analysis.

Our GL include some features that need further specification. First, we did choose a contrast-enhanced CT scan as basis for delineation, since the WG agreed that it should be considered, the reference imaging to delineate CTV on. Dealing with specific features, similarly to Xu et al. [19], after revision of the JGCA LNs description, we specified that the proper location for LNs 16a1 [23] is placed posteriorly to the diaphragmatic pillars (instead of anteriorly). Moreover, we are among the few to show LNs 19 boundaries (among the GL selected by literature, only Cellini et al. previously did the same, although through a more general approach [25]). Another peculiar feature of our GL is the formal acceptance of some adjacent LNs overlap due to margin expansion by the respective reference vessel, produced by the topographic anatomical variability in vessel distribution for UGItc [10]. That is accepted since is not clinically affecting the final extension of the generated CTV.

The points of strength of this GL are: (1) the specific reference assigned to the JGCA LNs classification, (2) the collaborative contribution of ROs with both radiologists and surgeons, to clarify the anatomical and radiological issues dealing with each LNs, (3) the multiple, repeated alternation of on-line and live meeting to go through the issues regarding each LNs, (4) the concomitant availability of boundary description and CT atlas and the interactive atlas to train the RO's delineation skills. The educational ESTRO program for Fellowship in Anatomic deLineation and CONtouring (FALCON) aims to improve interactive teaching and increase contouring homogeneity by comparing individual contours with endorsed guidelines or expert opinions [1]. Over the past years it was widely applied to support the ESTRO delineation courses and contouring workshops. The combination of traditional teaching methods with a web-based contouring and contour-analysis platform led to a significant reduction in delineation variability before and after the administered course [33]. Moreover, the FALCON EduCase platform was particularly applied to online delineation workshops to permit the training of geographically dispersed participants. These workshops, held using the FALCON EduCase platform, offered (beside training) initial contouring harmonization and allowed qualitative and quantitative delineation assessment of the involved participants [34]. For these reasons, we applied such platform to enable WG participants to simultaneously contour, double-check, and discuss delineations from different countries. These opportunities provided the chance for remote meetings and allowed additional remote work of each participant to the same case delineation, before and after the live-meetings. Moreover it permitted to release a self-training guideline tool.

Limitations of our GL are represented by the above mentioned and well-known intrinsic anatomical variability, limiting the generalizability of the indications for each clinical case, particularly for patients with anatomical variances of the main vessels. Moreover, only a preoperative CT-based clinical case was investigated, thus possibly limiting the adaptability of our GL in some postoperative settings. That choice was made to firstly support future CTV GL, clinical investigation, and routine clinical care of preoperative and definitive clinical presentations. The preoperative setting is the most reliable to understand anatomical boundaries. Moreover the preoperative setting is more likely to be investigated for future significant prospective clinical trials about UGItc (rather than the postoperative one), and an available GL can prevent variability. Finally, the postoperative setting indication for LNs boundaries can be consequently derived by adaptation of the preoperative indication, thus establishing the preoperative setting first, seems a priority.

Future research should focus on validating the reproducibility of CTV delineation based on our GL and on investigating their potential impact for treatment planning and clinical outcome. Moreover, our GL could be the basis for developing a MR-based anatomical atlas for future clinical and scientific purpose. Finally, the GL adaptation to the postoperative setting in multiple UGItc would be useful.

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Author's contribution

VV project concept, project planning; VV and MV writing committee chair and supervision; FC project manager, paper drafting, FALCON Case administrator; AR radiological anatomy supervision, writing committee for radiology; TBB writing committee for radiation oncology, focus on pancreatic cancer pertinence nodal areas; FR writing committee for radiation oncology, focus on pancreatic cancer pertinence nodal areas; FG external referring for surgical anatomy, focus on liver vascular and biliary tract pertinence nodal areas; SA external referring for surgical anatomy, focus on pancreatic and splenic pertinence nodal areas; RM external referring for radiological anatomy, focus on pancreatic, liver and biliary tract pertinence nodal areas; FA external referring for surgical anatomy, focus on biliary tract pertinence nodal areas; CF external referring for surgical anatomy, focus on pancreatic pertinence nodal areas; VP external referring for surgical anatomy, focus on thoracic pertinence nodal areas; AGM reviewing committee of project and paper drafting; KH reviewing committee of project and paper drafting; SM external referring for surgical anatomy, focus on thoracic and para-diaphragmatic pertinence nodal areas; BDB writing committee for radiation oncology, focus on esophageal cancer pertinence nodal areas; OM writing committee for radiation oncology, focus on gastric cancer pertinence nodal areas; EG writing committee for radiation oncology, focus on biliary tract cancer pertinence nodal areas; CB ACROP project supervision and planning, reviewing committee of project and paper drafting; WA writing committee for general surgical anatomy, focus on thoracic, para-diaphragmatic, pancreatic/splenic, liver vascular and biliary tract pertinence nodal areas.

Conflict of interest statement

The authors declare that they have no competing interests.

None of the authors has any financial and personal relationships with other people or organisations that could inappropriately influence (bias) of this work.

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Appendix A. Supplementary data

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