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Original Article

Optimal delineation of the clinical target volume for thymomas in the post-resection setting: A multi-center study

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ABSTRACT

Background: The definition of the clinical target volume (CTV) for post-operative radiotherapy (PORT) for thymoma is largely unexplored. The aim of this study was to analyze the difference in CTV delineation between radiation oncologists (RTO) and surgeons.

Methods: This retrospective multi-center study enrolled 31 patients who underwent PORT for a thymoma from five hospitals. Three CTVs were delineated per patient: one CTV by the RTO, one CTV by the surgeon (blinded to the results of the RTO) and a joint CTV after collaboration. Volumes (cm^3), Hausdorff distances (HD) and Dice similarity coefficients (DSC) were analyzed.

Results: RTO delineated significantly bigger CTVs than surgeons (mean: 93.9 ± 63.1, versus 57.9 ± 61.3 cm^3, $p = 0.003$). Agreement was poor between RO and surgeons, with a low mean DSC (0.34 ± 0.21) and high mean HD of 4.5 (±2.2) cm. Collaborative delineation resulted in significantly smaller volumes compared to RTO (mean 57.1 ± 58.6 cm^3, $p < 0.001$). A mean volume of 18.9 (±38.1) cm^3 was included in joint contours, but missed by RTO. Conversely, a mean volume of 55.7 (±39.9) cm^3 was included in RTO's delineations, but not in the joint delineations.

Conclusions: To the best of our knowledge, this is the first study investigating CTV definition in thymoma. We demonstrated a significant variability between RTO and surgeons. Joint delineation prompted revisions in smaller CTV as well as favoring the surgeons' judgement, suggesting that surgeons provided relevant insight into other risk areas than RTO. We recommend a multidisciplinary approach to PORT for thymomas in clinical practice.

Radical thymectomy is the primary treatment for all types and stages of a thymic tumor. Completeness of surgical resection with adequate margins is considered the most important prognostic factor [1–3]. The resection status is defined as: no evidence of macroscopic and microscopic residual tumor (R0), evidence of microscopically tumor (R1) or macroscopic residual tumor (R2) within the resection margins [4]. According to the ESMO-guidelines, postoperative mediastinal radiotherapy (PORT) is advocated in thymomas with an R1-resection or Masaoka-Koga stage III/IVA. PORT in stage II thymomas remains controversial, but may be considered in B2/B3 thymomas with a R0-resection [5–8]. PORT is associated with a prolonged overall survival (OS) and recurrence-free survival (RFS), especially in stage III/IV thymomas [5,9,10]. Accurate delineation of tumor volumes is a time-consuming and crucial step in radiotherapy, but it is also the most susceptible to human error [11]. Radiation oncologists (RTOs) are often dependent on descriptive language used by other specialists, such as surgeons and radiologists [12]. Computed tomography (CT)-based planning is used to determine the clinical target volume (CTV). CTV is the area of the primary tumor plus a margin for microscopic tumor spread that is not visible on imaging [13,14]. In thymoma, the optimal postoperative CTV is not well-defined

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and different definitions are being used in clinical practice [13]. Furthermore, it is not clear yet what the role of the surgeon could be in the delineation of thymomas. Hypothetically, the surgeon has insight information of the areas at risk after thymectomy. The delineation of thymomas, and thus PORT, could be suboptimal if the RTO delineates without the surgeon. The aim of this multicenter study was to analyze a possible difference between RTOs and surgeons for the post-resection delineation of the CTV in patients with a thymoma.

Patients and methods

This multicenter, retrospective study re-evaluated existing imaging and clinical data of patients with a thymoma who underwent PORT after thymectomy. Five European centers participated in the study: Maastricht University Medical Center (MUMC) & Maastro Clinic, Erasmus University Medical Center Rotterdam, Antwerp University Hospital, University Hospital Leuven and Thorax Institute Curie Montsouris Paris. These five centers were chosen due to their experience with thymomas. The medical ethics committee (METC) of MUMC approved this study (METC number: 2019-1347), followed by local approval of METCs of the other four participating hospitals. Patient characteristics and imaging were anonymously collected by MUMC. Inclusion criteria were as follows: patients who had undergone a thymectomy for a thymoma and subsequently received adjuvant PORT and were >18 years old. Post-operative imaging, including a CT-scan, must have been available for analysis. Patients were excluded if they did not undergo a thymectomy with PORT, if there was an R2-resection (i.e., macroscopic residual disease), or in case of pathological outcomes other than a thymoma. Preferably, thymectomy was performed in the last 10 years but this was not strictly required. Thymomas were histologically classified by the WHO Histological Classification of Thymomas [15]. Tumor invasion was classified by the Masaoka-Koga Staging System and TNM Classification of Malignant Tumors [16]. Early-stage thymomas were defined as Masaoka-Koga stages I and II or TNM <T3N0M0. Advanced-stage thymomas were defined as Masaoka-Koga stages III and IV/ TNM $\geq$ T3N0M0. The five participating centers each appointed one pair of observers, consisting of an RTO and a thoracic surgeon, who had preferably performed the thymectomy. The thoracic surgeon was blinded to the initial delineation of the RTO and had to delineate the CTV, on the first post-operative planning CT-scan. Communication between the RTO and surgeon during delineation was prohibited to ensure blinding. It was permitted to use additional information during delineation, including clinical records, surgery and pathology reports, positions of surgical clips, other available pre-and post-operative imaging modalities, multidisciplinary team reports and interoperative videos. No specific delineation guidelines were provided. The surgeon was instructed to delineate the regions that were believed to be at risk. Subsequently, the surgeon and the RTO collaborated and jointly delineated another CTV. In total, three CTVs were collected per patient; the initial delineation of the radiation oncologist, the delineation of the surgeon and the joint delineation of the surgeon with the RTO (Fig. 1).

The mean volume (in cm^3) was defined as the average of all CTVs contoured for each patient per observer group (e.g., surgeons, RTO or both). Overlap was measured using the Dice similarity coefficient (DSC). DSC assesses the similarity between two contours by looking at the intersection relative to the union in 3D (Fig. 2A). A DSC = 0 indicates no overlap between two observers, whereas a DSC = 1 indicates complete overlap. In general, a value of >0.6 is considered good, whilst a value of >0.8 is very good [17,18]. Differences in surface dimensions and spatial relations between two contours were assessed using Hausdorff distances. The Hausdorff distances measures the maximum distance from one point in one contour to the closest point in the opposing contour in a single slice (Fig. 2B) [18]. The mean slice-wise Hausdorff distance (MSHD) averaged the maximum Euclidean distance to the nearest neighbor in a set of contours across all slices [19]. Higher HD values indicate greater distance and dissimilarity between the two contours.

Statistical analysis

Descriptive statistics were reported as mean, standard deviation (SD, ±), median and interquartile ranges (IQR). Statistical analysis was performed with SPSS statistical software (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). Statistical significance was considered with the probability value of $p < 0.05$. A paired t-test or Wilcoxon-signed rank test compared volumetric differences between all groups. MATLAB 2020a (The Mathworks Inc, Natick, MA, USA), a computing language, was used by physicists to create a technical algorithm. This algorithm permitted analysis of interobserver variations in CTV as well as the overlap (DSC), distance (HD) and mean slice-wise Hausdorff distance (MSHD) between contours.

Results

In total, 31 patients were enrolled in the study based on the inclusion criteria. Mean age was 56.7 (±11.4) years and there was an equal gender distribution. Thymectomies were performed between 2005 and 2020. The surgical technique varied across hospitals including a sternotomy in 17 patients (54.8%), robotic-assisted thoracoscopic surgery (RATS) in 11 patients (35.5%) and video-assisted thoracoscopic surgery (VATS) in 3 patients (9.7%). There was an equal distribution in early- and advanced stage thymomas. An R0 and R1 resection was performed in 25.8% and 74.2%, respectively. All analyzed scans were CT-scans and contrast was used in seven patients (22.6%). Mean time between thymectomy and the planning-CT was 51.7 (±29.0) days. PORT was performed with a mean dose of 57.3 (±4.4) Gy in 29.1 (±2.1) fractions. Nearly all patients received photon therapy, only one patient received proton therapy.

Five pairs of RTOs and surgeons independently delineated the CTV on planning CT-scans. Hereafter, each pair also jointly contoured the CTV. This resulted in a total of 93 CTVs. The CTV volume delineated per observer per individual patient is shown in Fig. 3. This figure displays volumetric differences between the delineations of RTOs, surgeons and the joint delineations. Due to small numbers it was not feasible to compare the five hospitals with each other. However, the observers of hospital B appeared to delineate more comparable volumes than the other hospitals. Furthermore, surgeons of hospital A tended to delineate small volumes. As shown in Fig. 4a, RTOs tended to delineate the largest volumes (mean: 93.9 ± 63.1 cm^3). Surgeons contoured significantly smaller volumes (mean: 57.9 ± 61.3 cm^3, $p = 0.003$). Collaborative delineation resulted in the smallest volumes (mean 57.1 ± 58.6 cm^3). While this was significantly different from the volume of the RTO ($p < 0.001$) there was no difference in volume between surgeons and the joint delineation ($p = 0.610$) (Fig. 4b). A mean volume of 18.9 (±38.1) cm^3 was included in joint contours, which was not delineated by RTO. Conversely, a mean volume of 45.3 (±28.9) cm^3 was included in RTOs delineations, but not in the joint delineations (Fig. 4c).

Overlap, expressed by DSC, was poor between the contours of surgeons and RTO (mean DSC 0.34; ±0.21) (Fig. 5a). Joint delineations overlapped only moderately with RTOs delineations (mean DSC 0.49 ± 0.16). A moderate overlap was found between the con-

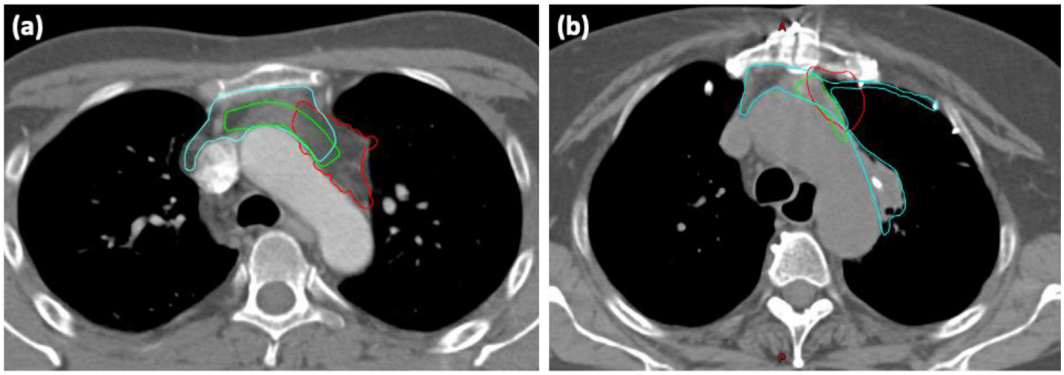
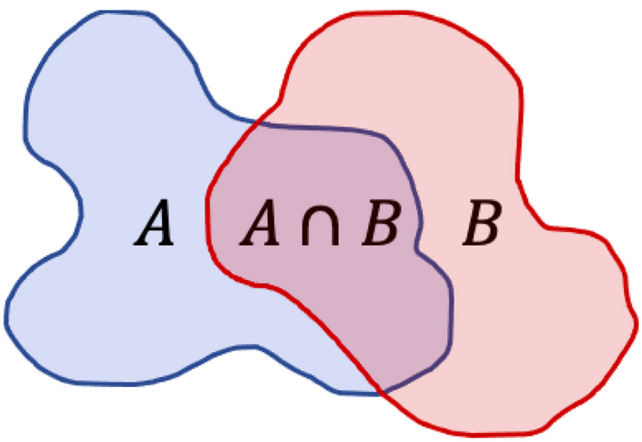
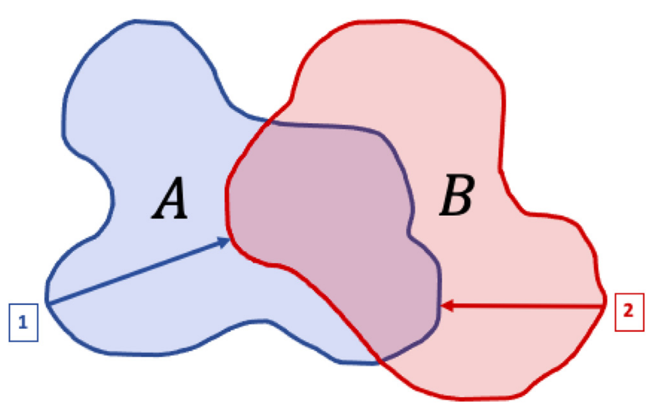


Fig. 1. Illustrative cases of interobserver variation in CTV delineation of a thymoma by a radiation oncologist (blue), surgeon (red) and both observers (green). (a) Axial CT-thorax image of patient 1, after robot-assisted thoracic surgery. (b) Axial CT-thorax image of patient 21, after a sternotomy. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article).



a

Fig. 2a. Illustration of the Dice similarity coefficient (DSC). The area of intersection of contour A (blue) and contour B (red) is depicted as A∩B. Higher DSC values indicate greater overlap and similarity between contours. Formula available in supplementary data. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article).



b

Fig. 2b. Illustration of the Hausdorff distance (HD). Arrow 1 depicts the maximum Euclidean distance of "reference" contour A to the nearest point in "test" contour B. Similarly, arrow 2 depicts the maximum Euclidean distance of "reference" contour B to the nearest point in "test" contour A. Formula available in supplementary data.

tours of surgeons and joint delineation with a mean DSC of 0.44 (±0.28). The largest HDs were observed between the volumes of RTOs and surgeons with a mean of 4.5 (±2.2) cm (Fig. 5b). Joint and RTOs delineations were also dissimilar with a mean HD of 4.2 (±2.3) cm. On the contrary, joint delineations were located closest to the contours of surgeons with a mean HD of 3.4 (±1.7) cm. Surgeons and RTO contoured disparate locations with a mean MSHD of 2.1 (±0.95) cm. Contours of RTOs and joint delineations were situated at a mean HD of 1.7 (±0.69) cm from each other. Nevertheless, across all slices, the greatest agreement was again reported between surgeons and joint delineations, with a mean HD of 1.5 (±0.90) cm.

Discussion

The aim of this multi-center study was to analyze differences between RTOs and surgeons in delineation of postoperative CTVs in thymoma patients, and whether joint delineations (RTO and surgeon together) yielded different CTVs. We concluded that RTOs delineated significantly larger CTVs compared with surgeons. Furthermore, the poor overlap of contours (measured by DSC) and the distance between volumes (measured by HD) between RTOs and surgeons resulted in a mean geographical miss of 19 cm^3. The bigger CTVs defined by RTOs therefore did not compensate for high-risk areas that were erroneously omitted. This multi-center study is, to our knowledge, the first to examine inter-specialty variability between RTOs and surgeons in the post-operative CTV delineation of thymomas.

We observed notable changes of CTVs after joint delineation. These joint delineations were smaller, and more closely located to the contours of the surgeons. This suggests that the knowledge provided by the surgeon is very helpful in guiding the radiation oncologist. However, the question still remains what the optimal definition of the CTV is. Historically, larger CTVs including the whole mediastinum were used, but later smaller volumes to encompass the high risk areas were advised [13]. In this study we considered the vision of the surgeon as the gold standard. This assumption is debatable, but because surgeons have seen to which extent a tumor was resected, including the locations of invasion, adhesion or reconstruction, they have the most knowledge to adequately define the zones at risk for microscopic spread. Furthermore this reduced CTV may potentially decrease the toxicity of PORT [20,21]. Our result are in line to earlier research suggesting that a desire to encompass the entire tumor, microscopic spread and other geometric uncertainties, along with less 3D anatomical-radiological knowledge, may explain why RTOs are prone to delineating larger volumes [22]. In our study, RTOs failed to delineate a mean volume of approximately 19 cm^3 that was included in joint contours. This may result in under-dosages of

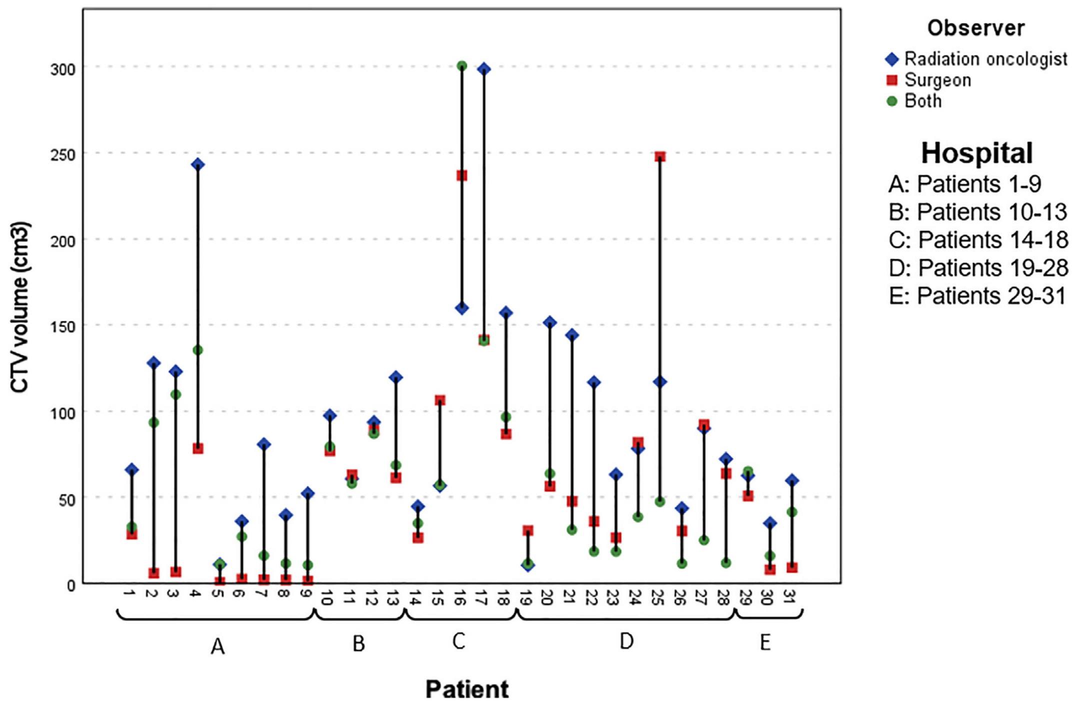


Fig. 3. Analysis of volumes. Scatterplot illustrating each clinical target volume (CTV) delineated by a radiation oncologist (blue), surgeon (red) or both observers (green) per individual patient. Radiation oncologists delineated larger volumes than surgeons in 24 out of 31 cases. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article).

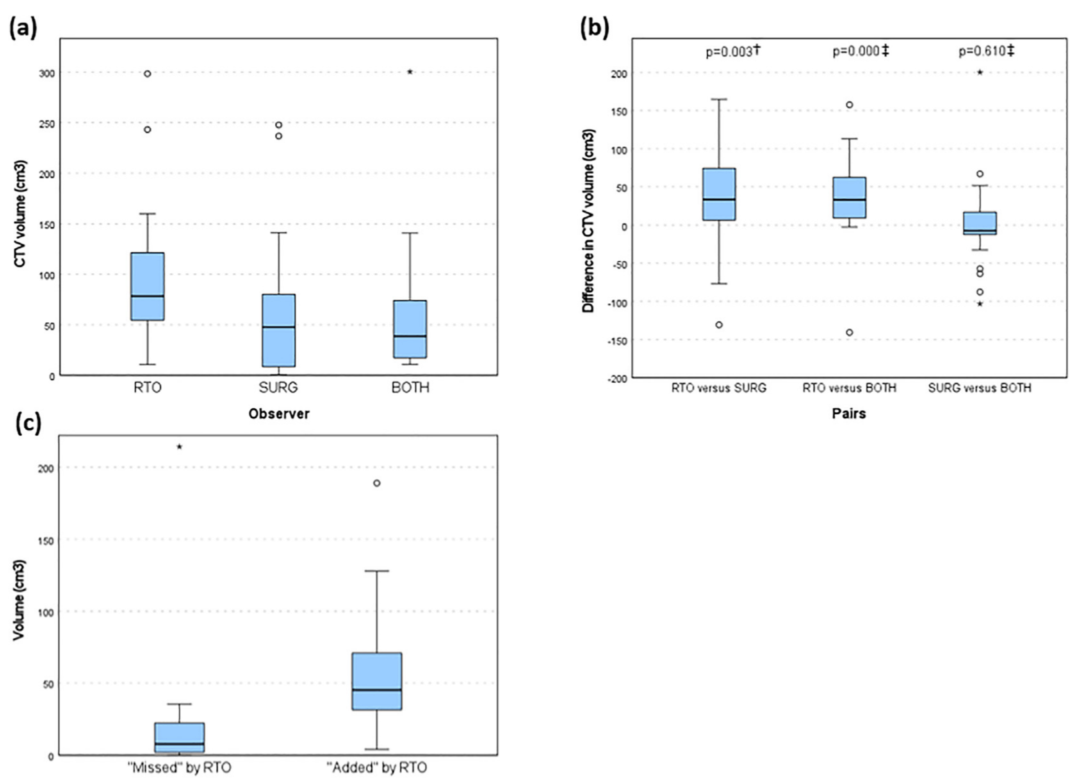


Fig. 4. (a) CTV contoured by each observer-group. Observer-groups include radiation oncologists (RTO), surgeons (SURG) and joint delineations (BOTH). (b) Differences in CTVs between observer-group. (c) Non-overlap volumes between RTOs and BOTH. It depicts the volume included in BOTH, but that was "missed" in RTO's and possibly under-contoured. Conversely, it also depicts the volume that was not included in BOTH, but that was "added" by RTOs and possibly over-contoured. Median values with 25th and 75th percentile range (box) and 1.5 times the interquartile range (whiskers) are shown. Outliers are marked by a circle (°). Extreme outliers are marked by a star (*). Paired *t*-test permitted (†); Wilcoxon signed-rank test used instead (‡).

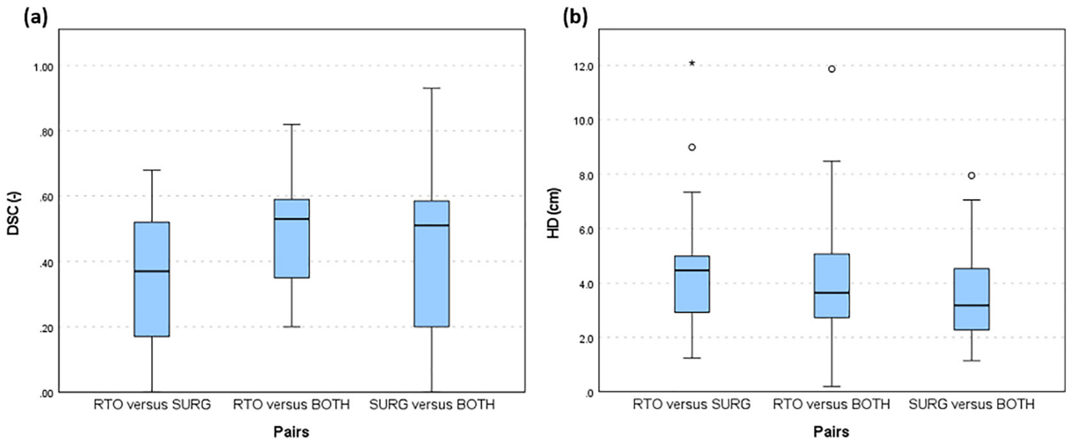


Fig. 5. (a) Dice similarity coefficient (DSC) and (b) Hausdorff distance (HD) between observer-groups, including radiation oncologists (RTO), surgeons (SURG) and both observers (BOTH). Median values with 25th and 75th percentile range (box) and 1.5 times the interquartile range (whiskers) are shown. Outlier are marked by a circle (°). Extreme outliers are marked by a star (*).

the joint CTV, and subsequently result in a higher risk for local relapse of thymomas. Local or pleural recurrences of thymomas are not uncommon, occurring in 10–30% of all-stage resected tumors [2,23,24]. The clinical impact of this inter-specialist variability was not examined by our study, but the results suggest that current definition of the postoperative CTV is suboptimal. Further research is required to analyze the impact of under-contouring and over-contouring, which could lead to differences in recurrences and toxicity, and ultimately overall survival. Increased CTV precision could benefit patient care by sparing surrounding organs "at risk" and thus preventing short- and long-term complications of PORT. In general, fewer complications are expected to be associated with preserved quality of life, increased return to work, and lowered healthcare costs. An optimal CTV also minimizes the risk of recurrence and maximizes survival benefit after irradiation [25,26]. A study by Mercieca et al. has reported that interprofessional collaboration (e.g., physicists, radiation oncologists, radiologists) greatly reduced interobserver variation in the gross tumor volume (GTV) delineation in lung cancer [27]. It led to the smallest mean volume, a decrease in erroneous delineations and an increased identification of positive lymph nodes. Furthermore, Vinod et al. reported that inter-observer variability in volume delineation can be reduced with the use of guidelines, provision of auto-contours and teaching [28]. In thymomas, only inter-observer variability between RTOs has been analyzed [11]. Currently, a lack of a standardized protocol for PORT in thymomas leads to only brief advice in international guidelines [5,8]. These results support our findings that a protocol and further research in optimal delineation of CTVs for thymomas in the post-resection setting is necessary.

This study comes with limitations. First, in each observer-group five radiation oncologists and five surgeons were recruited. Vinod et al. reported that the optimal number of observers and imaging datasets in studies examining inter-observer variability is uncertain. Therefore, we concluded that five pairs of observer-groups were sufficient for this study, although larger groups could possibly lead to more specific information among hospitals. Considering the rarity of thymomas and scarce eligibility of PORT, the small sample size of 31 patients was adequate for a pilot study. Second, this study could not ensure that the same RTO or surgeon delineated the initial CTV and the joint CTV. This can potentially lead to an extra layer of interobserver variability in volume delineation, which could have an impact on the results of this study. Due to the retrospective nature of this study, it was not possible to change to a more ideal method and the authors are aware of the less favored methodological circumstances. Besides that, this study reflects 'real-life practice' because in clinical practice it is uncommon that every time the same RTO and surgeon are together on the same delineations. This is the first study on this topic and it is important to share the results, but also the limitations and struggles, to support and optimize further research. The main goal was to analyze if there was a difference between the CTVs of RO and surgeon and the results of this study give answer to that question. Third, surgeons were possibly affected by recall bias, as sixteen thymectomies had been performed more than five years before enrollment in this study. On the other hand, surgeons are more likely to remember rare procedures, such as thymectomies, and it was permitted to use tools (e.g., operative reports, imaging) as a reminder throughout the delineation. As the same tools were available to the RTO, this cannot explain the observed differences. It is well possible that RTOs and surgeons previously already delineated CTVs together for some of their patients. This may well explain the smaller inter-specialty variability observed in some of the participating centers. Lastly, the level of experience of the observer, as well as their personal bias, training, familiarity with delineation software, and confidence, were not recorded and could lead to confounding. A larger prospective multicenter study is recommended to optimize the limitations of the current study. Ultimately our recommendation is to have specific radiation oncology and surgery tumor boards dedicated to a systematic and personalized delineation of target volumes for PORT in thymic tumors; such approach is currently part of the RADIO-RYTHMIC study, a phase III, randomized trial aiming at comparing PORT versus surveillance after complete resection of Masaoka-Koga stage IIb/III thymoma [29].

Conclusions

This study demonstrates that significant inter-specialty variability exists in target volume delineation of thymomas, contributing to uncertainty in CTV definition, possibly leading to larger CTVs and geographical misses. Delineation of post-operative thymoma volumes should not be done in isolation, joint contours with radiation oncologist and surgeons is preferred. Further research is required to improve the methodological circumstances and to assess whether multidisciplinary target volume delineation also improves long-term clinical- and oncological outcomes.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.10.007.

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