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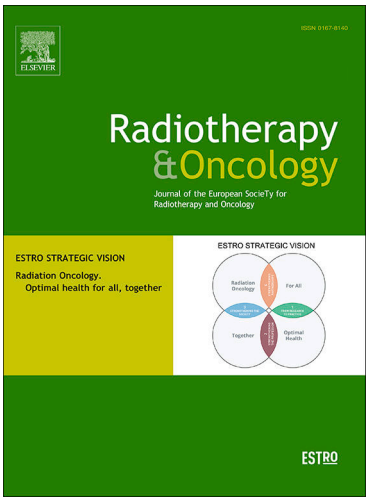

Guidelines

Highly conformal whole abdominopelvic radiotherapy: Consensus delineation guidelines from EpSSG and QUARTET

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Highly conformal whole abdominopelvic radiotherapy: consensus delineation guidelines from EpSSG and QUARTET

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Highly conformal whole abdominopelvic radiotherapy: consensus delineation guidelines from EpSSG and QUARTET

ABSTRACT

Purpose/Objective

Whole abdominopelvic radiotherapy (WAP-RT) is a complex treatment required for rare types of soft tissue sarcoma with peritoneal involvement. We present a consensus-based definition of the clinical target volume (CTVm_peritoneum) for WAP-RT for paediatric and adult patients.

Material/Methods

QUARTET clinician reviewers for the Frontline and Relapsed Rhabdomyosarcoma (FAR-RMS) Trial (NCT04625907) met between March and September 2024 to review the WAP-RT plans submitted for radiotherapy quality assurance. Variations in CTVm_peritoneum delineation were identified. Consensus was informed by literature and reached following the Nominal Group Technique.

Results

The most frequent variations in CTVm_peritoneum were at the cranial and caudal extent of the peritoneum, and the relation to adjacent organs at risk. The cranial limit is the diaphragmatic dome. A 4D-CT is recommended to identify the variation related to respiration, generating an internal target volume (ITVm_peritoneum). For cases without 4D-CT, the full respiratory excursion should be accounted for in the planning target volume (PTV) margins. The retroperitoneum should be excluded from the volume where not involved, using the iliac bifurcation as an anatomical surrogate landmark for the caudal extent. At the caudal limit of the peritoneum, the bladder should be entirely included, unless there is controlled bladder filling or adaptive protocols, when the bladder can be gradually excluded from the superior aspect of the symphysis pubis. The upper third of the rectum is included entirely, while only the anterior component of the middle third is included. Both kidneys and the surrounding perirenal fat are excluded. The liver surface is included in the volume, encompassing the gallbladder, porta hepatis, hepatic hilum, and the falciform ligament.

Conclusion

A consensus-based delineation guideline has been developed for CTVm/ ITVm_peritoneum for WAP-RT. The atlas will be implemented to support clinicians for FaR-RMS, future QUARTET trials, and will be of benefit for other metastatic sarcomas with peritoneal involvement, such as desmoplastic small round-cell tumours.

1. Introduction

The open Frontline and Relapsed Rhabdomyosarcoma (FaR-RMS) trial (NCT04625907, EudraCT: 2018-000515-24), developed and led by the European paediatric Soft Tissue Sarcoma Study Group (EpSSG), is an overarching study for patients with newly diagnosed and relapsed rhabdomyosarcoma, investigating multiple research questions related to chemotherapy, radiotherapy, tumour biology, and imaging [1].

Radiotherapy quality assurance (RTQA) is a requirement for all treating centres and patients included in the radiotherapy trial questions. This is facilitated through the Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials (QUARTET), a SIOP Europe project for RTQA in paediatric clinical trials [1,2]. Prospective RTQA with individual case reviews (ICR) is highly recommended for all trial patients receiving radiotherapy.

The protocol recommends delivering local therapy to metastatic sites, where feasible, including whole abdominopelvic radiotherapy (WAP-RT) for peritoneal involvement [3]. The Memorial Sloan Kettering Cancer Centre series reported favourable outcomes for those treated with aggressive surgical resection and WAP-RT. Based on this, the QUARTET-RTQA guidelines recommend a radiation dose for WAP-RT of 24 Gy in 16 fractions (or equivalent), followed by a boost to any focal disease, where identifiable [4].

Due to the rarity of WAP-RT indications in paediatric oncology, achieving consistency in target volume delineation can be particularly challenging, with the potential for significant variability in contouring approaches between different centres and clinicians. There are currently no published guidelines on WAP-RT contouring.

Here, we present the identified sources of variation in the delineation of the clinical target volume for the peritoneal cavity (CTVm_peritoneum) observed in the initial WAP-RT cases submitted to QUARTET, the resulting EpSSG Radiotherapy Committee consensus-based guidelines, and an evaluation of their application in two test cases. This initiative aims to produce supporting resources to be integrated into the FaR-RMS RTQA protocol, aiding radiation oncologists, investigators, and reviewers.

2. Materials and methods

2.1. Panel composition and study timeline

Between March and September 2024, a panel of 10 radiation oncologists from the EpSSG Radiotherapy Committee, representing 10 institutions across 8 European countries (Belgium, Denmark, France, Italy, the Netherlands, Norway, Spain, and the United Kingdom), participated in a consensus process following the Nominal Group Technique [5,6]. The panellists are all QUARTET clinician reviewers for the FaR-RMS trial, contributing their expertise and representing practice from across Europe.

The meetings and consensus process were coordinated and moderated by the QUARTET team to ensure a structured and standardised approach.

2.2.Identification of cases and sources of variation

A preliminary case-review meeting was held in March 2024. Patients' pseudonymised data were retrieved from the QUARTET database, which houses all submitted cases for ICR within the FaR-RMS trial. All patients undergoing WAP-RT were identified, and their plans were analysed to define variations in CTVm_peritoneum delineation:

- Unacceptable variation: significant (major) variation from the protocol, likely to impact clinical outcomes [7].
- Acceptable variation: minor variations from the protocol with no major clinical impact expected. It may require targeted education to prevent major deviation [7].

Variabilities in contouring approaches were systematically assessed, and sources of variation were categorised based on anatomical regions. A written summary of meeting outputs was circulated afterwards to panellists to support independent reflection and proposal drafting.

2.3.Consensus development process

A second QUARTET-EpSSG panel meeting took place in July 2024 to address the identified sources of variation. During the meeting panellists presented independently developed proposals in a round-robin format, followed by moderated clarification and consolidation of proposed recommendations [5,6].

The discussions were informed by existing literature on WAP-RT and relevant anatomy, with a particular focus on the relation of adjacent structures to the

boundaries of the peritoneal cavity, alongside the clinical experience of panel members.

Following discussion, proposed recommendations were rated by each panellist using a non-anonymous (open) agree/disagree vote, , with a round of voting for each proposal. Moderators were excluded by voting process. Consensus was defined when the prespecified ≥80% agreement was reached among participants. Statements not reaching the consensus threshold were to be refined, subjected to further discussion and re-voting.

2.4. Consensus validation and delineation testing

To validate the consensus recommendations and assess their applicability, two delineation test cases were selected by the QUARTET team to encompass different clinical scenarios, including anatomical variations in patient size and sex. The CTVm_peritoneum was delineated on the planning CT, according to the newly established guidelines, by a radiation oncologist (the first author) using Velocity (Varian Medical Systems, Palo Alto, CA). The test-case datasets (CT images with structure set) were circulated to all panellists in advance of the validation meeting to support independent review.

In September 2024, the panel reunited for a final meeting to review the contouring of the test cases, allowing for further clarifications and, if needed, re-voting. Feedback from this session was incorporated into the final guidelines, ensuring feasibility and clinical relevance.

3. Results

A total of five cases from the FaR-RMS trial, undergoing WAP-RT from January 2021 (opening of radiotherapy randomisation) to March 2024, were submitted to QUARTET for ICR and were all included in the analysis (Figure 1).

Among these, two cases had major deviations in target delineation, while two cases had minor deviations.

Overall, the analysis revealed a lack of consistency in:

- Cranial extent of the volume at the diaphragmatic dome, and approaches used to account for respiratory motion.
- Caudal extent of the volume at the pelvic peritoneal reflections (e.g. recto-uterine or rectovescical pouches), and strategies adopted to account for organs' filling variability.

- Coverage of retroperitoneal structures, and exclusion of kidneys, perirenal fat, and the great vessels.
- Coverage of hepatic surface, peritoneal ligaments, and recesses, and exclusion of liver parenchyma.

These findings are summarised in Figure 2, which illustrates the variations identified across the cases.

After the collation of the independent reviewer reflections, the following consensus statements were proposed, discussed and approved between panellists to enhance standardisation in CTVm_peritoneum delineation. Each of these statements reached the prespecified ≥80% agreement threshold on the first vote, and no re-voting was required.

I. Cranial extent

- CTVm_peritoneum encompasses the abdominal surface of the diaphragmatic dome.

II. Defining the retroperitoneal space

- The oesophagus, aorta, inferior vena cava (subhepatic), psoas muscle, kidneys, and perirenal fat (if visible) should be excluded from CTVm_peritoneum.
- The retroperitoneum extends from the diaphragmatic crus down to the pelvic inlet [8]. The iliac bifurcations can serve as a reference point for defining the caudal extent to aid CTVm_peritoneum delineation.

III. Nodal irradiation

- In the presence of para-aortic or iliac nodal involvement, the involved site nodal clinical target volume (CTVn) should be delineated separately.

IV. The Liver surface

- In absence of metastatic liver involvement, only the liver surface is included in CTVm_peritoneum, as it is covered by peritoneum, with the gallbladder, porta hepatis, hepatic hilum, and falciform ligament (where this can be identified) to be included. To ensure the liver surface is adequately covered, it is recommended that a rim of at least 5.0-7.5 mm should be used.

V. The relationship of the Bladder to the peritoneum

- If bladder filling protocols and daily on-treatment image guidance protocols are used, the bladder can be progressively excluded from the target volume in the caudal direction, starting at the superior aspect of the symphysis pubis.
- In absence of such protocols, the bladder should be entirely included to ensure adequate coverage.

VI. The relationship of the Rectum to the peritoneum

- The upper third of the rectum should be fully included in CTVm_peritoneum.
- Only the anterior portion of the middle third should be covered. The coverage is graduated between the upper third of the rectum (full coverage) and the lower third of the rectum (excluded) but must ensure the inclusion of the space between the anterior rectal wall and the bladder, prostate, or uterus.
- At the level of the middle third, if the rectal filling variability poses reproducibility concerns, the posterior boundary of the volume may be extended into the rectal lumen.
- The lower third of the rectum is excluded as it is outside the peritoneum.

VII. Motion management

- Four-dimensional computed tomography (4D-CT) imaging is recommended to identify the maximum inspiration point and phases of respiration, to ensure adequate coverage throughout the respiratory cycle, generating an ITVm_peritoneum.
- Where 4D-CT is unavailable, the PTV margin should be larger and include an additional motion component beyond that for set up, based on the individual centre's treatment technique, immobilisation and image guidance protocols, factoring in the patient's age and size, to ensure coverage of the full extent of the respiratory cycle.

To confirm the consensus-based guidelines, two test cases were selected, out of the 5 cases included in the study, to evaluate the applicability and robustness of the delineation recommendations. The first test case involved a 2-year-old female patient with rhabdomyosarcoma of the central pelvis, with peritoneal and subpleural metastases (Figures 3 and 4). The second test case involved a 10-year-old male patient with rhabdomyosarcoma of the right lower chest wall, with peritoneal and nodal metastases (Figure 5). These cases were chosen to represent

a variety of clinical scenarios (such as the involvement of para-aortic nodal stations), and anatomical variations across age and sex.

Feedback from these test cases helped refine the delineation recommendations, explicitly stating to ensure the inclusion of the falciform ligament when identifiable. The qualitative review supported validation of the recommendations and confirmed their practicality and relevance in the context of rhabdomyosarcoma radiotherapy treatments.

4. Discussion

WAP-RT is recommended for the treatment of children and young people with sarcomas such as rhabdomyosarcoma, desmoplastic small round-cell tumours, and Ewing sarcomas with primary or metastatic peritoneal involvement, and also Wilms tumours, where there is intracavitary rupture or peritoneal dissemination [4,9–12]. However, there are no published delineation guidelines. This work addresses this omission.

To achieve the best long-term results for survivors of childhood malignancies, more highly conformal radiotherapy techniques are being employed routinely, and contouring atlases for complex targets such as the peritoneum are essential to improve consistency between different clinicians, particularly for rare indications such as this.

Traditionally delivered using conventional radiotherapy techniques with two (AP/PA) photon fields, WAP-RT encompassed large anatomical regions, leading to significant exposure of surrounding healthy tissues, with the potential to cause severe side effects, including acute gastrointestinal and hematologic toxicities [13,14]. Furthermore, organ shielding techniques used to protect critical structures such as the liver and the kidneys resulted in significant dose inhomogeneity and inadequate target coverage [15,16].

With the development of advanced image-guided, rotational intensity-modulated radiotherapy (IMRT) techniques, more precise targeting of the peritoneal cavity became feasible, facilitating considerable sparing of surrounding normal tissues through inverse planning [17]. Early experiences with IMRT for WAP-RT demonstrated the ability to reduce the dose to the OARs, decreasing the risk of myelosuppression and nephrotoxicity, while improving target volume coverage and uniformity [15,16,18–21]. Moreover, the integration of 4D-CT and potentially motion management with respiratory gating too, allowed for a better definition of

volumes and more accurate delivery throughout the patient's breathing cycle [16,22].

Despite the evolution of technical planning approaches for WAP-RT, there remains a significant gap in the literature regarding the definition of peritoneal target volumes, and this has undoubtedly contributed to the variation observed in the FaR-RMS trial cases presented in this work. These variations, together with concerns related to administering radiotherapy to large volumes in children, underscore the need for standardised delineation guidelines. The introduction of consensus-based delineation guidelines in other areas has been demonstrated to have a positive impact in clinical practice, reducing inter-observer variability for clinical target volumes [23].

Recognising this need, the QUARTET clinician reviewers for the FaR-RMS Trial, from the EpSSG Radiotherapy Committee, produced this consensus-based definition of the clinical target volume for WAP-RT in paediatric patients with rhabdomyosarcoma. The method preferred to develop the consensus was the Nominal Technique Group, which was considered the most appropriate due to the limited published evidence for this specific topic and the contribution of a restricted group of experts. The initial identification of areas requiring clarification was based on five cases submitted for QUARTET ICR; although limited, this dataset reflects the clinical reality of this rare indication.

The consensus guidelines aim not only to present a strict anatomical description but to integrate practical considerations, creating an easy-to-implement guideline for centres internationally. Anatomical landmarks that ensure coverage of areas at risk of local failure, such as the recto-uterine or the recto-vesical pouches, and peritoneal reflections around the liver (for which the FaR-RMS trial mandatory constraint is D50% ≤ 28Gy), are provided [24,25]. Furthermore, confirmation of exclusion of the retroperitoneal space will facilitate a reduction in radiation exposure to the kidneys (which mandatory constraint is D50% ≤ 15-18 Gy for combined kidneys) and to adjacent skeletal structures, including pelvic bones and femoral heads/hip growth plates, which is particularly relevant for children and pre-pubertal adolescents prior to completion of bone growth. The integration of advanced imaging modalities such as 4D-CT, to aid the generation of an ITVm_peritoneum, is emphasised, to ensure consistent target coverage across all respiratory phases. Similarly, bladder filling protocols and adaptive radiotherapy strategies are identified as potentially offering the opportunity for further

minimising dose exposure to adjacent pelvic OARs, although these can be challenging to implement for young children.

The resulting consensus-based guidelines have been developed to support radiotherapy treatments for rhabdomyosarcoma patients with primary or metastatic peritoneal involvement; however, with the appropriate clinical judgment, it is anticipated they could also be applied for other sarcoma or paediatric malignancies requiring WAP-RT.

5. Conclusion

A consensus-based clinical target volume definition for WAP-RT has been developed by a panel of 10 radiation oncologists from the EpSSG Radiotherapy Committee, in collaboration with QUARTET.

The produced resource will be integrated into the FaR-RMS RTQA guidelines, with supporting documentation provided for trial investigators, radiation oncologists, and reviewers alike, to improve standardisation and treatment consistency.

Further validation will be performed through prospective monitoring of WAP RT cases within the FAR-RMS trial and other trials utilising the QUARTET framework.

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Conflict of interest statement

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.

CRediT author statement

Maria Chiara Lo Greco, Sarah M. Kelly, Data curation; Formal analysis; Investigation; Maria Chiara Lo Greco, Sarah M. Kelly, Henry C. Maneville: Conceptualisation, Methodology, Writing - original draft; All Authors: Supervision, Validation, Writing - review & editing.

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Figure 1 Overview of patients enrolled in the FaR-RMS trial treated with WAP-RT, in coronal (A) and sagittal (B) view. Columns correspond to individual patients with CTVm_peritoneum in blue for case 1, orange for case 2, green for case 3, pink for case 4 and red for case 5.

Figure 2 Variation in CTVm_peritoneum delineation within five FaR-RMS patients treated with WAP-RT in axial view. Columns correspond to individual patients with CTVm_peritoneum in blue for case 1, orange for case 2, green for case 3, pink for case 4 and red for case 5. Rows show representative levels selected to illustrate key sources of variability: (A) the most cranial extent of CTVm_peritoneum, (B and C) upper abdominal levels demonstrating variability in inclusion of adjacent structures (retroperitoneum, liver and kidneys), and (D and E) the most caudal extent of CTVm_peritoneum.

Figure 3 Axial CT slices spanning the cranio–caudal extent of test case 1, illustrating the full length of CTVm_peritoneum and its relationship to selected organs-at-risk and vessels. Panels A–T progress from cranial to caudal. CTVm_peritoneum is shown in pink; additional contours indicate the liver (white), kidneys (left: orange; right: light blue), aorta (red), inferior vena cava (dark blue), iliac vessels (purple), bladder (yellow), and rectum (green).

Figure 4 Coronal (A and B) and sagittal (C and D) views throughout the whole length of test case n. 1. In Figure A, guides are positioned on the highest slice, showing the diaphragmatic dome. Figure B highlights the exclusion of the perirenal space. In Figure C, guides are on the lowest slice, excluding the retroperitoneum. Figure D uses guides to indicate the upper aspect of the pubic symphysis, serving as a bony landmark to define the caudal limit of the volume. CTVm_peritoneum is shown in pink; additional contours indicate the liver (white), kidneys (left: orange; right: light blue), aorta (red), inferior vena cava (dark blue), iliac vessels (purple), bladder (yellow), and rectum (green).

Figure 5: Axial view of test case n. 2 for nodal delineation. CTVm_peritoneum is shown in pink; additional contours indicate the liver (white), kidneys (left: orange; right: light blue), aorta (red), inferior vena cava (dark blue), iliac vessels (purple), and CTVn (black).

Highlights

- Cranially, the CTVm_peritoneum encompasses the abdominal surface of the diaphragm.
- Caudally, it includes the bladder and the upper/anterior middle third of the rectum.
- The retroperitoneal space should be excluded, down to the iliac bifurcations.
- The liver surface should be included with a rim of at least 5.0-7.5 mm.
- 4D-CT imaging is recommended to generate an ITVm_peritoneum.

Declaration of interests

☒ 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.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Figure 1 panel A

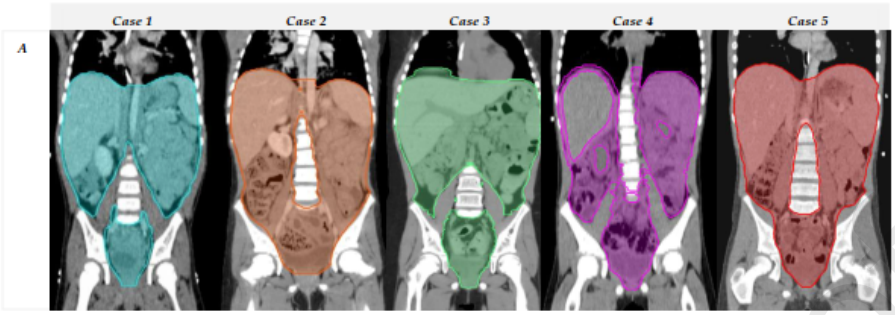

Figure 1 panel B

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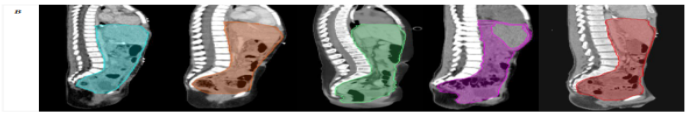

Figure 2 panel A

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Figure 2 panel B

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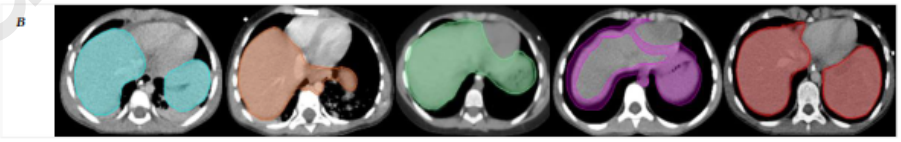

Figure 2 panel C

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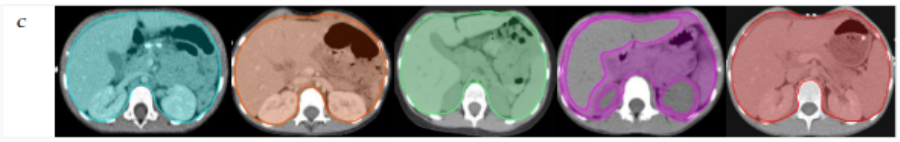

Figure 2 panel D

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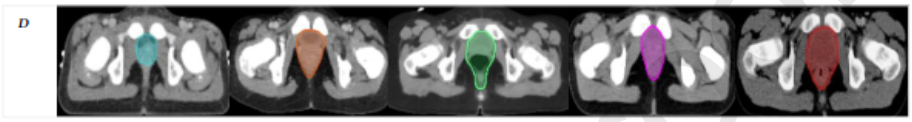

Figure 2 panel E

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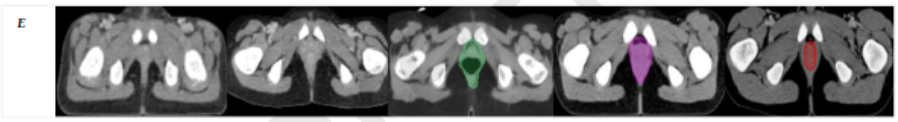

Figure 3

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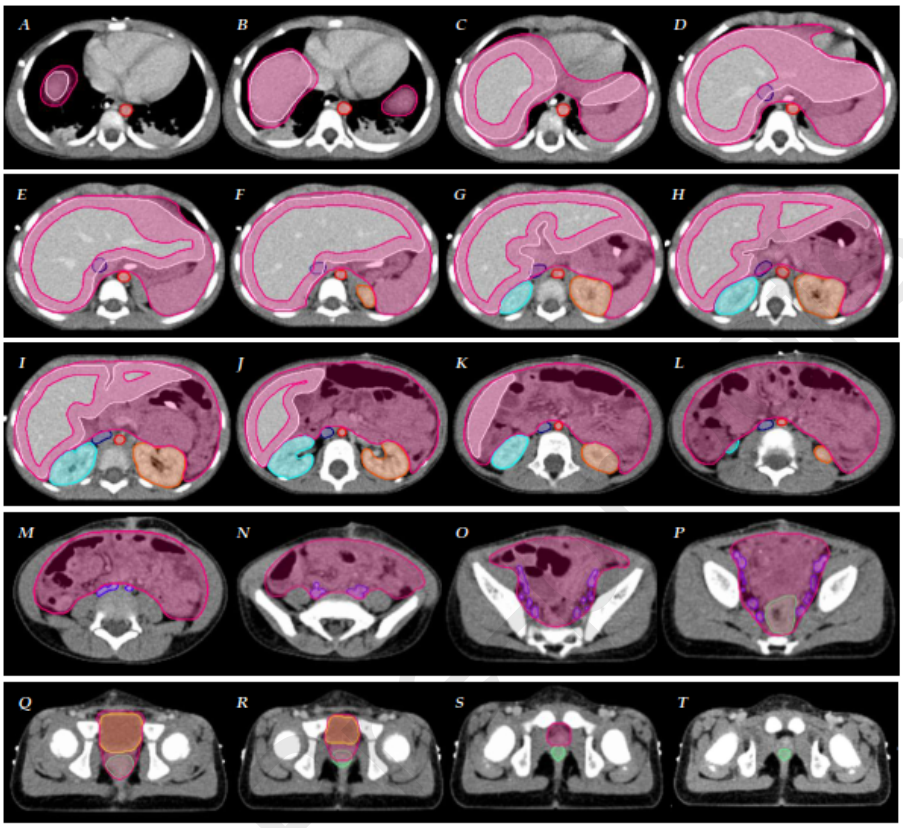

Figure 4

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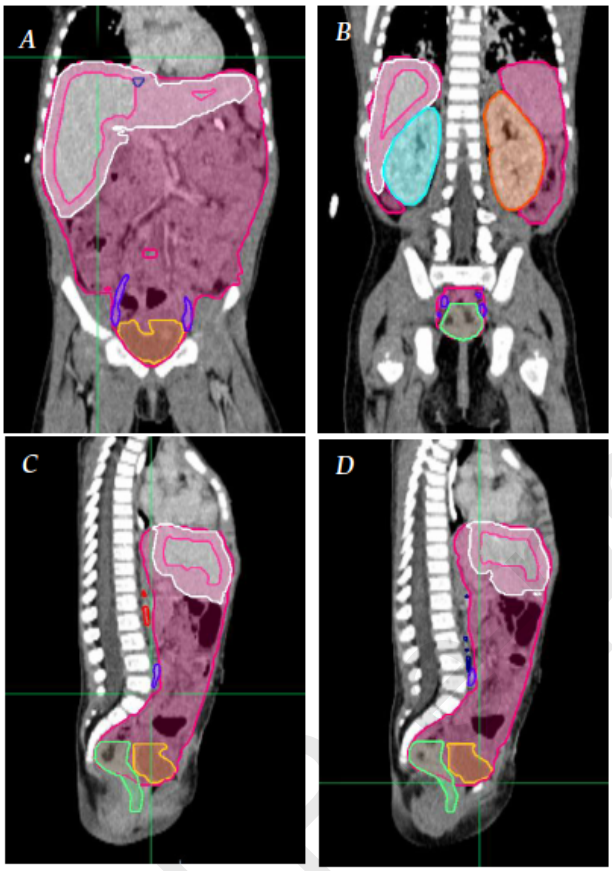

Figure 5

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