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ESTRO technical guideline: intensity modulated radiotherapy and image guided radiotherapy for rectal cancer

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ABSTRACT

Introduction: Intensity Modulated Radiotherapy (IMRT) and Image Guided Radiotherapy (IGRT) have become an integral part of standard care for rectal cancer, but evidence-based detailed guidance is lacking to support its clinical implementation and use. This European SocieTy for Radiotherapy and Oncology (ESTRO) technical guideline aimed to assess the available evidence and provide recommendations for their use in rectal cancer treatment.

Materials and methods: The ESTRO Lower Gastrointestinal (GI) Cancer guidelines subcommittee formed a writing panel to address key questions (KQs) on the application of IMRT and IGRT in rectal cancer management. The panel conducted a literature review and where evidence was insufficient, expert consensus was used.

Results: The writing panel (2 RTTs, 2 medical physics experts, 3 radiation oncologists) identified 14 KQs. Recommendations were based on low to moderate evidence and/or expert consensus. Supine positioning is preferred for patient comfort and stability. Comfortable full bladder should be used. For OAR delineation and dose optimization, mandatory (Bladder, Bowel Cavity, Femoral Heads) and optional OAR were defined. Auto-delineation is supported for OAR and can be considered for target volumes. Dose metrics for minimizing gastrointestinal and genitourinary toxicity were identified. Auto-planning tools and MR-only workflows are feasible, both require proper QA. Uncertainties from setup and target volume shape variations must be accounted for with appropriately defined margins. Daily volumetric image guidance is recommended for treatment verification.

Conclusion: This ESTRO technical guideline for the use of IMRT and IGRT for rectal cancer was developed to support development and implementation into clinics.

Introduction

The standard treatment strategy for many rectal cancer patients includes the use of radiotherapy, either short course radiotherapy (SCRT, 25 Gy in 5 fractions) or long course radiotherapy (LCRT, 45–50.4 Gy in 25–28 fractions, 1.8–2.0 Gy per fraction, with optional tumour boost) with concomitant fluorouracil-based chemotherapy. This will most commonly be in the pre-operative setting, where it improves local control in cases of intermediate risk, resectable cancer and facilitates downstaging in high-risk borderline resectable or initially unresectable tumours [1,2]. However, (chemo)radiotherapy is also increasingly being used to facilitate non-operative management [3–5] of early rectal cancers [6,7]. This may allow patients to avoid the substantial morbidity and potential diminished quality of life associated with surgery, but may impose greater demands on the quality of radiotherapy.

Two key techniques are essential for modern radiotherapy planning and delivery: (1) Intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT), which allow for precise dose shaping using steep dose gradients around the clinical target volume (CTV), and (2) image guided radiotherapy (IGRT (2D/3D)), which visualizes patients anatomy (2D or 3D, bony anatomy and/or soft tissue) and thus improves treatment accuracy. Combining IMRT and IGRT enables optimized planning target volume (PTV) margins. These techniques have the potential to significantly reduce radiation exposure to healthy tissues, particularly bladder and bowel, without compromising target volume coverage. Retrospective studies have indicated that IMRT may reduce acute toxicity for rectal cancer patients undergoing preoperative (chemo) radiotherapy [8], although the picture has been nuanced by more recent publications [9]. IMRT and IGRT combined facilitate the delivery of simultaneous integrated boosts (SIB) [10–12]. Both techniques are currently widely available, and are part of standard treatment strategies for rectal cancer radiotherapy in many countries [11,13]. A recent UK survey reported 95% of centres treated all patients with IMRT [14].

However, there are limited practical and technical international guidelines to support the implementation of IMRT and IGRT for rectal cancer. Some national guidance exists [1,11,13] but there is a lack of published evidence-based guidelines. Therefore, the European SocieTy for Radiotherapy and Oncology (ESTRO) and its Lower GI guidelines subcommittee tasked an initiative to develop a technical guideline to support the clinical application of IMRT and IGRT. This manuscript presents the technical guideline, reviewing the available literature and providing recommendations for effective implementation to maximize clinical benefits.

Materials and methods

This guideline, along with its scope and the composition of the writing and review panel, were approved by the ESTRO Guidelines Committee. The composition of the writing panel aimed for diversity in discipline, experience and a balance between academic and non-

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academic radiotherapy centres. The writing panel comprised an international group of experts, including radiation oncologists (RO) (n = 3), medical physics experts (MPE) (n = 2), and radiation therapists (RTT) (n = 2). The panel was chaired by AA and RdJ.

The scope and content of this guideline has been structured around a series of Key Questions (KQs). KQs were developed based on structured discussions within the writing group during online meetings, focused on the radiotherapy workflow and with particular emphasis on IMRT and IGRT. Resulting KQs were reviewed and approved by the Lower GI guidelines committee (ESTRO). Clinical and Gross target volume definitions were excluded [15]. Adaptive radiotherapy, such as library of plans or online adaptive radiotherapy, were also excluded on the basis that these techniques and technologies are not (yet) widely available.

A comprehensive literature review (PubMed only) was conducted in accordance with PRISMA guidelines to address the KQs. A standardized set of search terms and inclusion/exclusion criteria were applied across all KQs to identify papers on rectal cancer and (chemo)radiotherapy. General inclusion criteria allowed for both systematic reviews and original research articles and studies conducted in both the preoperative and non-operative management setting. Additional search terms were specific to each KQ; see Supplement A for full details. The KQ-specific literature searches were performed in PubMed between November 2023 and June 2025. Supplement A details whether abstracts and/or grey literature were considered for each KQ.

The findings from the literature reviews served as the basis for the recommendations for each KQ. The quality of evidence and strength of recommendations were assessed following the methodology established by the American Society for Radiation Oncology (ASTRO) (ASTRO Methodology Guide – V1: 5/2019). In cases where the available literature was insufficient, expert consensus was achieved through discussion and/or voting. Consensus was defined as at least a majority agreement ($n \geq 4$). When the group was unanimous in its opinion, we labelled the strength of recommendation as 'strong'.

All members of the writing group contributed to the final manuscript, which underwent peer review by an independent reading panel. The final version was approved by all members of the writing group.

Results

The writing panel identified 14 KQs. The findings from these KQs (based on literature review and/or expert consensus) were synthesized into recommendations, which are summarized in Table 1, as well as visualized in a Flowchart (Fig. 1).

KQ 1) What is the optimal patient immobilization with respect to reproducibility, stability and dose to organs at risk?

The prone position with a bellyboard device was commonly used during the era of 2D and simple 3D treatment planning (three or four field box techniques) to reduce dose to normal tissue by displacing the small bowel from the target volume [16–19], with or without bladder distension [20].

The transition to IMRT / VMAT and IGRT, and the associated optimisation of plan conformality and PTV margins, has allowed for a reduction in planned bowel dose. Studies have investigated whether the prone position with a bellyboard device is still beneficial in this context. Most studies have found that it can reduce radiation dose to the small bowel further [21–29], but not all publications support this conclusion [30,31]. Bladder filling / distension also appear to maintain some benefit in this setting [26,28]. However, these results are based on relatively small populations and on comparison of treatment planning that does not take into account inter- and intrafraction motion (both setup variation and soft tissue changes).

Treatment position also impacts setup reproducibility and stability. Reproducibility appears superior in the supine position relative to the prone position (with or without bellyboard) [22,26,29,30,32]. Literature on intrafraction motion is limited, but the supine position is also favoured with respect to stability [33]. Finally, the supine position is

Table 1
Overview of key questions and recommendations.

	Key Questions	Recommendations	Strength	Level of Evidence
1.	What is the optimal patient positioning with respect to reproducibility, stability and dose to OAR?	• The supine position should be the first option for treatment position to enhance patient comfort, compliance and stability. • For individual patients where reduction of bowel dose is the primary concern, prone position on bellyboard should be an alternative option.	Strong	Low/ expert consensus
2.	What is the optimal regimen of patient preparation (bowel and bladder)?	• A patient preparation protocol should be used for a comfortable full bladder for planning and treatment (300–500 ml, 30–45 prior to imaging/ treatment). Patients should be educated on maintaining hydration status for both planning and treatment. • Strategies should be used to minimise flatus/faeces in the rectum for planning and treatment. An assessment of rectal diameter should be performed to ensure the CT planning scan is representative of patient anatomy.	Strong	Low/ expert consensus
3.	What are the mandatory and optional OAR to be outlined to support treatment planning and evaluation?	Mandatory OAR: • Bladder • Bowel Cavity • Femoral Heads Recommended OAR: • Vagina • External Genitalia • Penile Bulb • Anal Sphincter • Sacral Bones • Stoma (when within 1 cm of PTV in cranio-caudal direction)	Strong	Expert consensus
4.	Which consensus guidelines are there on the definition of OARs to support their outlining?	• Consensus guidelines for nomenclature and outlining of OAR should be used to enhance safety and improve quality for clinical practice as well as to enable data pooling. For standardized nomenclature, AAPM TG-263 is recommended; for outlining of OARs, see Table 2 for recommendations.	Strong	Expert consensus
5.	Can auto-delineation be used	• Auto-delineation can be used for OAR segmentation, with	Conditional	Low/ expert consensus

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Table 1 (*continued*)

	Key Questions	Recommendations	Strength	Level of Evidence
	for target volumes and/or OAR?	significant time-reduction benefits. • Auto-delineation can be considered for target volume segmentation. • When implementing consider both qualitative acceptability criteria (e.g. geometric accuracy, dosimetric impact) and outcomes assessments (e.g. actions to be taken for corrections); with subsequent use dependent on both case-specific QA and routine model QA.		
6.	What are the mandatory and optimal dose levels and metrics to consider for OAR, in order to minimize both acute and late toxicity?	• Dose to small bowel loops or bowel cavity should be limited to prevent acute and late GI toxicity. A range of optimisation objectives covering low to high dose levels are recommended. • The bowel cavity, or a comparable volume (such as peritoneal space), should be used for plan optimization, irrespective of the volume used for plan evaluation and reporting. • Dose to bladder should be limited, with a particular focus on limiting $V_{30\text{-}35Gy}$ to prevent acute toxicity. • For any other OAR outlined for an individual patient, dose should be reviewed as part of plan evaluation and prescription, and any patient-specific considerations should be recorded.	Strong	Low/ expert consensus
7.	Which dose metrics are to be considered for target dose evaluation?	• Radiotherapy treatment planning should aim to cover the planning target volume for primary tumour, involved lymph nodes, and elective volumes with 95% of the prescription dose, while minimising hotspots. • If delivering a SIB to tumour or involved nodes, this should be as conformal as possible, minimising spill-over of high dose into surrounding elective volumes.	Strong	Expert consensus
8.	How should dose to OAR and target volumes be prioritized during treatment plan optimization and evaluation?	• In general, dose to the target volume should take precedence over dose to OAR, although this prioritization may be adjusted for individual patients. • When prioritization changes, the applied registration strategy for daily IGRT should align accordingly.	Strong	Expert consensus
9.	Are there any specific technical considerations to be made regarding IMRT planning?	• Guidance provided separately in the main text and Table 4.	–	–
10.	Can auto planning solutions add value to IMRT planning, and what is the required QA?	• Commercially available auto-planning solutions can be used to improve the OAR sparing and increase the time efficiency and consistency of IMRT planning. • When used, verify and monitor local clinical performance continuously.	Conditional	Low
11.	What is the optimal method to calculate and report dose?	• Dose should be calculated and reported in dose-to-medium (D_m) where possible. • Special care should be taken when comparing D_m with dose-to-water (D_w) in cortical bone. It is not recommended to convert D_m to D_w (dose to water in medium, $D_{w,m}$) as this will result in poorer agreement with either D_w and D_m.	Strong	Expert consensus
12.	Is an MRI only workflow feasible using (commercially available) sCT for treatment planning?	• Commercially available sCT generation software can be used to generate sCT for dose calculation in an MR-only workflow. • MRI or sCT can be used as reference image for position verification in an MR-only workflow for rectal cancer; but additional QA may be needed due to the lack of native support in commercial software.	Conditional	Moderate/ expert consensus
13.	How are large are setup and target volume shape uncertainties?	• Systematic and random errors in setup and target volume shape variation are	Strong	Moderate

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Table 1 (*continued*)

	Key Questions	Recommendations	Strength	Level of Evidence
		substantial, even with daily image guidance, and should be accounted for in target volume margins. • The required margin should be defined separately for the primary tumour, involved lymph nodes, mesorectum (upper and lower) and further elective volumes (extra-fascial lymph nodes).		
14.	What is the optimal IGRT protocol to verify dose delivery?	• Daily volumetric imaging (i.e., Conebeam-CT/3D-MV) should be used to correct systematic and random setup errors by matching the bony structures as well as to evaluate the position of target volumes and OAR. • Supporting protocols (e.g., traffic light) should be used for image evaluation and decision making.	Strong	Moderate/ expert consensus

Recommendations are based on evaluation of multiple factors including the quality of evidence (QoE), individual study quality, and expert consensus, all of which inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments (ASTRO methodology guide). In cases where the available literature was insufficient, expert consensus was achieved through discussion and/or voting. Consensus was defined as at least a majority agreement ($n \geq 4$). When the group was unanimous in its opinion, we labelled the strength of recommendation as 'strong'.

Abbreviations: Image guided Radiotherapy (IGRT); Intensity Modulated Radiotherapy (IMRT); Organ(s) at Risk (OAR); Quality Assurance (QA); Gastro-intestinal (GI); Magnetic Resonance Imaging (MRI); Synthetic Computed Tomography (sCT); Simultaneous Integrated Boost (SIB).

documented as superior in terms of patient comfort; especially for frail patients, post-surgical cases, and patients with stomas [22,27,30].

The expert consensus is unanimously to use the supine position as the first choice prioritizing factors such as interfraction setup reproducibility, intrafraction stability as well as patient comfort. However, if minimizing small bowel dose is the only or primary objective the prone position with a bellyboard device is still optimal when using IMRT/VMAT.

KQ 2) What is the optimal regimen of patient preparation (bowel and bladder)?

Bowel and bladder filling can change considerably between treatment planning and delivery, and between individual treatment fractions [34,35]. However, there are limited data to support a specific bowel or bladder preparation protocol.

Theoretically, a (comfortable) full bladder pushes small bowel away from the target volume, thus minimising dose to the anterior part of the bladder and small bowel. To enhance bladder volume consistency throughout radiotherapy, it is recommended (expert consensus, unanimously) to provide patients with structured education and clear drinking instructions to ensure optimal hydration and a comfortable full bladder during both planning and treatment sessions (300–500 ml, 30–45 min prior)[11]. However, factors such as chemotherapy or medications may affect hydration status and thus bladder filling. Ultrasound scanners to assess bladder volume are very accurate and can assist in optimizing bladder volume just prior to treatment but may be logistically challenging [36,37]. Volumetric imaging is useful for anatomical assessment and volume prediction [38]. Some studies describe bladder volume control via catheter irrigation [39,40], and bladder volumes can decrease over the course of treatment [36,37,40].

Patients should be advised to empty their bowels before planning and treatment to reduce target volume deformation and unnecessary organ(s) at risk (OAR) dose. The rectum should not be extended (e.g. diameter should not exceed 4 cm [11]) at the planning stage to ensure that planning imaging is representative of reproducible anatomy throughout the duration of treatment (expert consensus, unanimously). Possible solutions to reduce the variability include allowing patients to pass gas or empty their bowels before proceeding; review of rectum diameter on scout imaging before full scan; review of the rectum diameter on the diagnostic imaging to assess the consistency of the rectal size and filling over time (and hence the feasibility of minimizing the diameter through interventions).

KQ 3) What are mandatory and optional OAR to be outlined to support treatment planning and evaluation?

Outlining of normal tissue as OAR may be for several purposes; including dose plan optimisation and evaluation, reporting of OAR dose for individual patients (even where no clear dose constraints exist), and to support long-term evidence generation. The first two considerations are the main focus of the current guidance.

Due to insufficient and inconsistent guidance in the literature, the writing panel conducted a formal voting process to achieve expert consensus on OAR for delineation (see Supplement B).

The OAR classified as mandatory for delineation were: *Bladder* (Unanimously), *Bowel Cavity* (Majority Agreement), *Femoral Heads* (Unanimously). Several definitions of Bowel Cavity were discussed, including 'bowel bag' as defined by the EMBRACE group (peritoneal cavity containing bowel loops, following the outer contour of visible bowel loops) [41], and 'bowel bag' from the RTOG atlas (abdominal contents excluding muscle, bones and non-GI normal structures) [42]. The writing panel agreed that the mandatory Bowel Cavity OAR should encompass all anatomy which may potentially contain bowel loops during treatment delivery, in line with the RTOG 'bowel bag' definition (see also KQ 6) and 'Spc_Bowel' described by Mir et al [43].

The OAR classified as recommended for delineation were (all decided with Majority Agreement): *External Genitalia*, *Vagina*, *Penile Bulb*, *Anal Sphincter*, *Sacral Bones*, and *Stoma* (applicable only when located within 1 cm of the PTV in the cranio-caudal direction).

The OAR classified as optional for delineation were (all decided with Majority Agreement): *Prostate & Seminal Vesicles*, *Ovaries*, *Uterus & Cervix, Lumbosacral Plexus*, *Diverticulum* (defined as part of the bowel that ends in the stoma), *Inguinal Area*.

An additional round of voting was conducted to determine the recommendations for OAR delineation in specific clinical scenarios. In these scenarios, the panel aimed to highlight additional OAR that may warrant delineation beyond those classified as mandatory. These were: Intention to boost either the primary tumour (GTV) (*Vagina* and *Anal Sphincter*) or clinically involved lymph nodes (*Sacral Bones* and *Lumbosacral Plexus*), intention for up front organ preservation (*Anal Sphincter*), intention for administering Total Neoadjuvant Treatment (*Bone Marrow*). For an overview see also Table 2.

Finally, the writing panel acknowledges that certain clinical scenarios and factors (such as patient age, frailty, or fertility preservation) can require complex decision making, and covering all scenarios is outside the scope of this current guideline. The panel also identified the rectum wall itself as a potential OAR in the context of organ preservation, but could not provide recommendations on its use due to a lack of literature and clinical experience with plan optimisation and evaluation strategies.

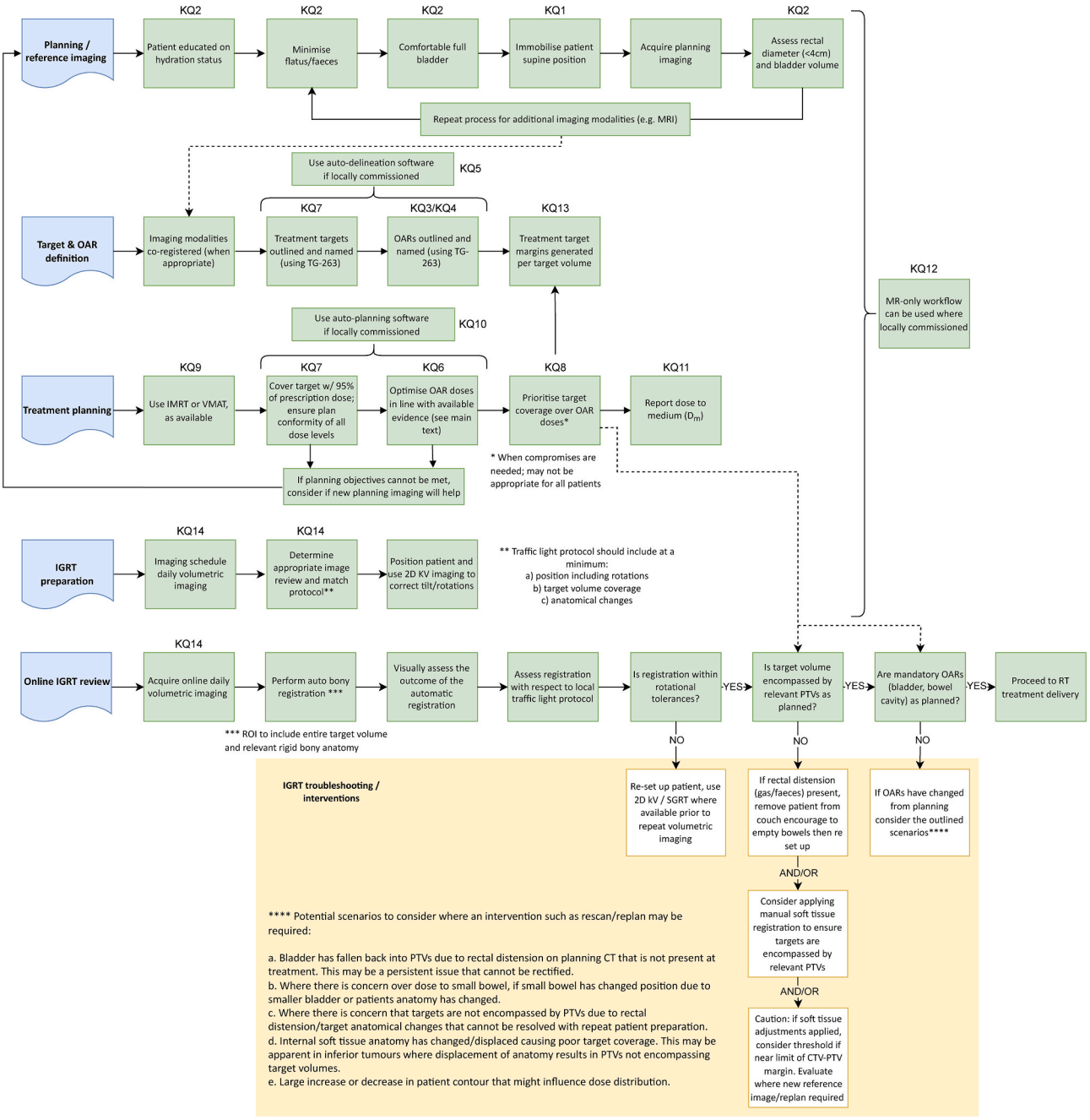

Fig. 1.

KQ 4) Which consensus guidelines are there on the definition of OAR to support their outlining?

A comprehensive understanding of normal tissue dose response is essential for optimal radiotherapy treatment planning. However, there is a significant knowledge gap, particularly regarding IMRT and VMAT, with only limited data available (see also KQ6). One contributing factor to this gap is the variability in delineation of OAR across clinical practice and research studies. Such inconsistencies not only hinder the comparability of dose volume metrics and their correlation with treatment outcomes within and between studies, but also impact clinical outcomes in routine practice.

The adoption of standardized delineation guidelines for normal tissues enhances the consistency and accuracy of radiotherapy, leading to improved clinical outcomes and reduced toxicity [44,45]. Additionally, the implementation of standardized nomenclature as in AAPM TG263 facilitates automation within clinical departments and supports wider research [46]. It is therefore recommended (expert consensus, unanimously) to use consensus guidelines for delineation as well as standardized nomenclature.

A review of existing consensus guidelines was conducted to identify standardized recommendations for outlining OAR in rectal cancer radiotherapy. Key OAR, as defined by expert consensus in KQ3 and their recommended consensus guidelines, are summarized in Table 2 [11,42,43,47–51].

KQ 5) Can auto-segmentation be used for target volumes and/or OAR?

Auto-segmentation is a promising tool for increased contouring consistency and resource savings across radiotherapy [52]. For rectal cancer, literature indicates that auto-segmentation can be used for relevant target volume and OAR segmentation [53–59] with evidence of significant time reduction as a benefit after implementation

Table 2
Overview of organs at risk (OAR) with available guidelines.

OAR	Standardised nomenclature (TG-263)	Reference and description
Mandatory		
Bladder	Bladder	The bladder should be contoured in entirety from base to dome. The lateral extent is the outer bladder wall [42,43].
Femoral heads (left / right)	Femur_Head_R/L	The structure includes the ball of the femur, femoral neck, greater trochanter, and proximal shaft to the caudal limit of the lesser trochanter [42,43].
Bowel cavity	Spc_Bowel*	Contour abdominal contents. Inferiorly from the most inferior small or large bowel loop (excluding rectum). Contour to 2 cm superior to PTV. Exclude: CTV, muscles and major vasculature (common, internal and external iliac vessels) and subtract bladder and uterus (if relevant) from structure.[11,42,43]
Recommended		
Stoma bag	Bag_Ostomy	No consensus guideline available. Should be used as an avoidance structure.
Genitals	Genitals	The female genitals structure encompasses the clitoris, labia major and minora, mons pubis, and the surrounding fat. The male genitals structure encompasses the entire penis, scrotum, perineal body, and the surrounding fat. Both structures extend laterally to the inguinal creases [43,47].
Penile bulb	PenileBulb	The penile bulb is the portion of the bulbous spongiosum of the penis immediately caudal to the genito-urinary diaphragm. The structure is normally 9–10 mm in the cranial-caudal direction. The contour should not continue in to the shaft of the penis [42,43,51].
Sacral bone	Bone_Sacrum*	No consensus guideline available.
Anal sphincter	Sphincter_Anal	No consensus guidelines available. Visuals see Arias et al. [48]. About 1 cm under the last contrast in the rectal ampulla.
Vagina	Vagina	The vagina is a central, muscular tube, approximately 7–9 cm in length, connecting the cervix or vaginal vault to the vulva [50,51].
Optional		
Bone marrow	BoneMarrow	No consensus guideline available as there is no consensus in delineation in the dose–response literature.
Cervix	Cervix	No consensus guideline available.
Diverticulum	Diverticulum*	No consensus guideline available.
Inguinal area	Spc_Inguinal*	Defined as the skin fold. No consensus guideline available. Should be used as an avoidance structure.
Ovaries and fallopian tubes (left / right)	Adnexa_R/L	Ovaries and fallopian tubes [42,50].
Prostate, Seminal vesicles	Prostate; SeminalVesc	Inferiorly from its apex and superiorly to its base. Entire seminal vesicles including those slices that also have prostate identified [42].
Uterus	Uterus	No consensus guideline available.
Where lymph nodes are boosted:		
Lumbosacral Plexus	SacralPlex	The lumbosacral plexus should be contoured from the L4 nerve root to the cranial most portion of the femoral neck [43,49].

*No standardized nomenclature available (American Association of Physicists in Medicine (AAPM) Task Group (TG) report 263); suggested naming provided.

[57,58,60–67]. The systematic literature search did not identify any prospective multicentre clinical implementation studies in the context of radiotherapy for rectal cancer. Existing publications are retrospective in nature and were predominantly conducted in single centre settings, identifying a significant evidence limitation. For most published studies, the number of patients used to train and validate the auto-segmentation models aligned with recommendations [68]. Training sets for these models typically ranged from 50 to 100 patients and testing datasets included at least 20 patients [54–57,59,64,66,67,69–74].

The majority of studies used human observer contours as the ground truth and most reported on in-house models rather than commercial ones. The reasons for this preference were not clear, but may be due to financial reasons, data sharing restrictions or academic incentives. Additionally, commercial systems will contain pre-set models which will have been pre-trained on external datasets, thus not necessarily reflecting local practice.

Published data indicate that for both OAR and target volume, the auto-segmentation solutions evaluated provide acceptable and satisfactory results with considerable time savings [54,55,61–63,65,67,69,75–77]. Additionally, studies evaluating end-users' preferences found that auto-segmentation was preferred in 40–52% of cases versus a human-made segmentation [66,72]. A few authors investigated the target volume or OAR only, while others considered both [54–57,59]. Papers specifically reporting on rectal cancer target volumes evaluated GTV delineation [64,70,72,76], elective CTV volumes [56,58,66,73,77] or primary tumour CTV. However, a large number of publications did not specify the target volume category they were addressing. There were no papers advocating against the use of auto-segmentation tools, either commercial or in-house, as long as structures are being evaluated and adjusted when necessary.

Overall, the limited evidence available supports the use of auto-segmentation for OAR and both elective and primary target volumes. Additionally, the use of auto-segmentation may increase the number of OAR evaluated in routine clinical practice. For implementation of auto-segmentation, qualitative acceptability criteria (e.g. geometric accuracy, dosimetric impact) and outcomes assessments (e.g. actions to be taken for corrections) are needed [60]. Both case specific QA and routine model QA should be used. Clinically implemented models need to be periodically recommissioned, but thresholds are not yet settled in the literature on when to prompt/initiate recommissioning [68].

KQ 6) What are the dose levels and metrics to consider for OAR, in order to minimize both acute and late toxicity?

Understanding normal tissue dose response and dose volume effects is essential for IMRT optimisation and evaluation. Most available data for radiotherapy for rectal cancer are based on 3D-CRT, with limited evidence in the IMRT or VMAT setting. It is unclear if findings from 3D-CRT are generalizable to IMRT, where the DVH correlations from 3D-CRT may be broken. Additionally, data are largely from LCRT, with almost none for SCRT.

The relationship between dose to the small bowel and acute gastrointestinal toxicity during preoperative LCRT has been extensively studied; see Supplement Table 1 and the 2019 review by Holyoake et al [78]. There is evidence to support a correlation between the volume of individual small bowel loops receiving dose levels from 5 Gy to 45 Gy (V_{5Gy} to V_{45Gy}) and acute diarrhoea, with no clear single dose level cut off

identified. Most studies of 3D-CRT found strongest associations with toxicity for low dose volumes ($V_{10\text{-}15Gy}$), but this may be an artefact of the statistical analyses [79] and DVH data collinearity. Conversely, limited data from VMAT patients found the strongest association with higher dose volumes (V_{45Gy}) [80]. Similarly, comparative studies of small bowel loops and peritoneal space as OAR with 3D-CRT [81] may not be generalizable to IMRT planning either. Very limited data is available on the association between dose to small bowel loops and late gastrointestinal toxicity [82,83]. A single large study (n = 486 patients) found the strongest relationship for V_{30Gy}, and recommended to keep small bowel $V_{30Gy} < 200$ cc (5% risk grade 3 +) or < 300 cc (10% risk grade 3 +). Consequently, optimization objectives should cover a range of dose levels, with priority given to limiting medium to high dose volumes (≥30 Gy) to limit late toxicity.

Most available data are based on the outlining of small bowel, being defined as individual bowel loops, rather than a more general 'bowel cavity' or 'peritoneal space' [81,84]. Given the significant interfractional movement of individual loops [85], the actual dose delivered to OAR may differ from the planned dose [86]. Data from whole pelvis prostate cancer IMRT indicate that treatment plans optimized with a peritoneal space / 'pelvis cavity' OAR are significantly more robust to interfractional bowel position variations in terms of the OAR dose delivered. Therefore, the bowel cavity, or a comparable volume, should be used for plan optimization, irrespective of the volume used for plan evaluation and reporting. Dose optimization to individual bowel loops may have to be considered when delivering a high dose boost.

Limited literature has explored the relationship between whole bladder dose and acute cystitis during LCRT (Supplement Table 1). One large retrospective analysis, based on a cohort of patients of which approximately one third were treated with IMRT, suggests that limiting $V_{30\text{-}35Gy}$ may reduce acute toxicity [87]. For late toxicity to bladder, there is a lack of data regarding dose volume effects, precluding specific recommendations on dose thresholds. Expert consensus (unanimously) agreed that dose to the bladder should be limited with a particular focus on limiting V30-35 Gy to prevent acute toxicity.

For other mandatory or recommended OAR (KQ3), data on dose response and dose volume relationships are scarce. The most well studied normal tissue, bone marrow, has inconsistent findings, hampering the establishment of clear optimization criteria (Supplement Table 1). For any other OAR outlined for an individual patient, dose should be reviewed as part of plan evaluation and prescription, and any patient specific considerations should be recorded.

The writing panel acknowledges that the definition of OAR dose constraints for IMRT treatment planning is highly dependent on clinical scenario and the acceptable risk for a giving patient/patient group. The UK RCR Rectal Cancer IMRT Guidance provides some guidance, primarily based on single institution experience [11].

KQ 7) Which dose metrics are to be considered for target dose evaluation?

IMRT plan optimisation for rectal cancer generally aims to deliver a homogenous dose prescription to the target volume(s); potentially with multiple different prescriptions to different volumes, as in the case of SIB delivery. Suggested planning objectives for target volumes were established through expert consensus, in line with general guidelines on IMRT planning and delivery [88], and informed by the UK Guidance [11]. Table 3 summarises the recommendations, using the recommended AAPM TG263 nomenclature [46]. In particular, note the suggested objectives for SIB delivery, ensuring evaluation of high dose conformality and minimising spillover of high dose into surrounding elective volumes.

KQ 8) How should dose to OAR and target volumes be prioritized during treatment plan optimization and evaluation?

Treatment plan optimisation and evaluation balances optimal target coverage with minimisation of dose to OAR, often necessitating compromises between the two objectives. The writing panel agreed (unanimous consensus) that the primary objective for standard preoperative radiotherapy for rectal cancer is to ensure adequate coverage of the GTV and CTV, to achieve effective tumour control with limited normal tissue exposure. The writing panel acknowledges that for individual patients and/or individual cases it will be at the treating physician discretion to prioritize an OAR over the target volume.

Table 3
Target Volume Metrics, with standardised nomenclature according to American Association of Physicists in Medicine (AAPM) Task Group (TG) report 263.

Target volume	Standardised nomenclature (TG-263)	Dose metric	Objective†
Gross tumour, involved nodes, and clinical target volumes	GTVp, GTVn, CTVp, CTVn, CTVe*	Avoid cold spots in GTV / CTV target volumes; e.g. keep these volumes covered by 95% isodose. For plan evaluation, e.g. use V95%≥99%	
Planning target volume for primary tumour and involved lymph nodes (where relevant)	PTVp, PTVn	$D_{99\%}$	≥90%
		$D_{95\%}$	≥95%
		$D_{50\%}$	= 100% ± 2%
		$D_{2\%}$	≤105%
Planning target volume for elective targets	PTVe*	$D_{99\%}$	≥90%
		$D_{95\%}$	≥95%
		$D_{50\%}$	= 100% ± 2%
		Avoid dose ≥ 105% away from any SIB volumes	
Evaluation structure when delivering simultaneously integrated boost (SIB)	PTVe minus (PTVp&n + 5 mm)	Minimise volume receiving 107% of the elective volume prescription dose. For plan evaluation, e.g. use $V_{107\%}$<15%	

† For dose measures (D_{xx}), all percentages are relative to the prescription dose for the volume in question.
* TG 263 does not have a recommended nomenclature for elective volumes. We propose using 'CTVe' and 'PTVe', or, alternatively, where there is no risk of ambiguity, simply 'CTV' and 'PTV'.
Abbreviations: Gross Tumour Volume (GTV); Clinical Target Volume (CTV); Planning Target Volume (PTV); Dose to XX% of the volume ($D_{xx\%}$).

Whenever OAR constraints cannot be met due to unfavourable anatomy captured on the planning imaging, assessment should include if repeat planning imaging could improve the OAR constraints, see also KQ 2. The applied IGRT protocol should be in line with the planning prioritizations, see KQ14.

KQ 9) Are there any specific technical considerations to be made regarding IMRT planning?

The existing literature on IMRT planning for rectal cancer was reviewed, with a particular focus on papers reporting on technique comparisons, plan optimisation settings, and impact of contrast on optimisation. Key findings are summarised below, with specific tips and tricks based on the literature provided in Table 4 [25,89–105].

A number of studies have compared IMRT and VMAT planning and delivery techniques. In general, planning studies have found similar plan quality for IMRT compared to VMAT, with some inconsistencies in findings: For example, Shang et al. reported that OAR dose might be slightly better with IMRT [106], while Liu et al. [107] and Dunman et al. [108] found VMAT superior to IMRT with respect to target coverage and normal tissue sparing. Importantly, there is a clear and significant reduction in delivery time with VMAT compared to IMRT [92,106,108].

Recent literature, especially on newer treatment platforms, is sparse. Findings suggest that [109,110]. Studies reporting on helical tomotherapy planning and delivery indicate that it may be used to support normal tissue sparing [31], especially used in conduction with daily imaging [111].

It is worth noting that no studies were found with a direct comparison of plans from different treatment planning systems (TPS) with the same modality, treatment techniques, and planners. Consequently, it is

Table 4
Tips and tricks for optimisation of Intensity Modulated Radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), based on available literature.

IMRT optimisation	• Gantry angles avoiding anterior entry may be beneficial to keep OAR dose low (particularly bowel and bladder) [85] • Seven beam angles may provide a good compromise between dose conformality and complexity / delivery time [86], although fewer angles can also provide acceptable plans [87]
VMAT optimisation	• Dual arcs may allow one arc to focus on each lateral part of the target, sparing anterior organs at risk [88] o This may either be achieved by full dual arcs and avoidance volumes, or actively restricting the arcs to avoid anterior compartment [89] o A combination of an avoidance sector and a 'peritoneal space' avoidance volume might provide the best overall OAR sparing, at least for prone position [90] o Partial arcs give better and more robust dose distribution in the prone position, compared to full arcs [91] • Consider contracting the PTV used for optimisation away from the skin (see e.g. [92] • Lower beam energies (6MV) are generally sufficient to achieve good plan quality [93], but higher beam energies could potentially be relevant for large patients / deep-seated tumours of large volumes [94]
Bowel	• Small bowel dose should be actively included in plan optimisation [23] • Bowel motion: o Although small bowel motion leads to uncertainties in delivered dose [95], IMRT plans still provide reduction in dose to small bowel compared to 3D-CRT plans [96] o Day-to-day bowel loop movements are significantly greater than day-to-day variation for peritoneal space [95]
Bladder	• 'Manually' optimised IMRT plans might not fully result in optimised bladder dose [97 98]; this might require additional attention if not utilising an auto-planning solution
Contrast and density corrections	• The presence of oral contrast on planning imaging may impact dose distributions, in particularly PTV and bowel dose [99], although with other literature indicating negligible impact (around 1% in mean dose to various structures) [100]. The overall impact likely depends on timing of CT, type of contrast, amount of contrast and dilution • Intravenous contrast agent has minimal impact on dose distributions [99] • Plans cannot be assumed to be robust to variation in intestinal gas, with particular risk to target coverage [101] • For plan optimisation, override densities that are likely to be different during delivery (oral contrast, significant rectal gas). Consider rescan for treatment planning when imaging includes significant gas which is unlikely to be present during treatment

Abbreviations: Organs at risk (OAR); Planning Target Volume (PTV); Computed Tomography (CT).

unclear what can be gained from improved optimisation engines alone. However, multicentre pre-trial benchmarking studies indicate that considerable variations can be found between centres, with different TPS and planners, even with stringent planning guidelines [102,112,113]. This supports the use of intercentre benchmarking and peer QA for treatment planning, including in the setting of clinical trials.

If SIB to the primary tumour is prescribed, IMRT or VMAT can deliver this without a substantial increase in dose to OAR [92,114–118], while achieving a more homogeneous dose distribution [119]. Importantly, when delivering a SIB, plan evaluation should include a measure of high dose conformity [120].

KQ 10) Can auto-planning solutions add value to IMRT planning, and what is the required QA?

Auto-planning is being increasingly utilised in radiotherapy, with solutions ranging from algorithm/scripting-based approaches to full AI based dose prediction and mimicking [121,122]. For IMRT planning for rectal cancer, auto-planning solutions contribute to improved OAR sparing [123–128], enhanced time efficiency [123–125,129], and increased consistency [98,129]. With one exception [130], all identified studies focused on treatment planning for LCRT. Auto-planning predominantly reduced the mean dose, V_{30Gy} and V_{40Gy} to the bladder and small bowel while maintaining comparable target coverage, indicating improved dose fall off towards these OAR.

Among the various automated planning approaches for rectal cancer, knowledge based planning (KBP) was the most widely utilized [97,98,124,126,128–130], followed by template-based iterative optimization [127] and script based optimization [123]. While these auto-planning solutions are commercially available, they do require some degree of in-house configuration and are not immediately deployable without customization. The latter two methods do not require any initial planning data to configure the auto-planning solution but the generation of a KBP model requires a minimum number of treatment plans as training data. Expanding the model library can improve the performance of the KBP model and increase its geometric diversity and representativeness. However, the introduction of suboptimal plans into the knowledge base should be avoided as this as this could negatively affect plan quality. Replanning suboptimal plans, either manually by an experienced dosimetrist or using a first iteration of the model, is beneficial to the performance of the model [126,129].

Although the reviewed studies demonstrated consistent findings, they were all retrospective and limited to single centre investigations, highlighting a lack of prospective implementation studies. Consequently, it remains uncertain whether the positive results found in the retrospective studies hold true in prospective clinical practice. It is recommended that each institution rigorously evaluates and monitors the performance of its auto-planning solution (whether in house or commercial) in prospective clinical practice so that the model can be updated if necessary [68].

KQ 11) What is the optimal method to calculate and report dose?

Modern TPS systems support type-B (e.g., convolution/superposition) and type-C (e.g., Monte Carlo and Grid Based Boltzmann solver) algorithms that enable dose calculations in a reasonable time frame. Consequently, the use of type-A dose calculation algorithms in the treatment planning of rectal cancer is not justified [131].

While there is a lack of definitive evidence supporting a single preferred method of dose reporting, consensus guidelines from the Global Quality Assurance of Radiation Therapy Clinical Trials Harmonisation Group [132] and NRG Clinical Trials [133] recommend dose to medium (D_m) as the standard framework for dose reporting.

Despite the fact that many dose constraints for these OAR have been established in terms of dose to water (D_w), it remains advisable to report in D_m to maintain consistency with ongoing and future clinical trials (expert consensus). Evaluation of D_w may allow comparison to historical dose prescriptions and tolerance thresholds (including those reviewed in KQ6). However, although it is technically feasible and supported by certain TPS to convert D_m to D_w (i.e., dose-to-water in medium, $D_{w,m}$), this practice is not recommended, as studies indicate that $D_{w,m}$ exhibits poorer concordance with D_w when compared to D_m[132,133]. In particular, the dose in cortical bone may be up to 10% higher when reported in $D_{w,m}$ compared to D_m, whereas the difference between D_m and D_w is of the order of a few percent, with D_m predicting a lower dose.

KQ 12) Is an MRI only workflow feasible using (commercially available) synthetic CT (sCT) for treatment planning?

Magnetic resonance imaging (MRI) is increasingly used in treatment planning for rectal cancer, due to the superior soft tissue contrast, especially for target definition [134]. Consequently, there is increasing interest in MRI only workflows to eliminate the need for treatment planning specific CT imaging and its registration uncertainties with MRI. The 2019 systematic review by Bird et al. found no clinical evidence

supporting the implementation of an MRI only workflow for rectal cancer [135], but our search identified seven studies published since this review, assessing the performance of commercially available MRI only software for rectal cancer [136–143]. In all studies, the standard MRI scanning protocol was supplemented with MRI sequences specific to the sCT generation software used. These sequences need to cover all the anatomy required for radiotherapy treatment planning, which sometimes requires two linked acquisitions to be stitched together offline into a single sequence to achieve sufficient superior-inferior scan length [136]. These sequences are optimised to minimise geometric distortions, and the geometric accuracy is routinely verified [137].

There is moderate evidence supporting the safe use of sCT for dose calculation in an MRI only workflow, with dose differences of less than 1% compared to planning CT across various imaging systems and commercially available sCT generation software [138,139,141–143]. However, some studies have reported a systematic overestimation of PTV dose [139,143] and general DVH differences [141]. These differences may be attributed to the handling of air pockets within the rectum by commercial software [139,143] or to the relative electron density curve that is applied to the generated sCT's HU values [141]. It is therefore recommended that the accuracy of a centre's local sCT generation technique is quantified during commissioning [137].

There is also moderate evidence to support the use of MRI or sCT as a reference image for position verification, demonstrating comparable results to CT, with systematic effects on Conebeam-CT (CBCT) registration below 1 mm and 0.5° [136,138–140,143]. However, commercial software currently lacks native support for using MRI or sCT as reference images, necessitating additional processing steps that can increase complexity [136,140]. Institutions should perform quality assurance on these processes to mitigate the associated risks.

In addition to improving the patient experience, patient comfort during MRI simulation should be optimised (expert consensus, unanimously) to minimize motion artifacts as well as minimizing inter- and intrafraction motion during treatment. This may be achieved using both earplugs and headphones, music for all patients, blankets to provide warmth, scanning of patients in the feet first position, and additional staff focus on providing information about the details of the MRI scan, particularly the scan time [144].

KQ 13) What are the setup and target volume shape uncertainties?

Understanding uncertainties in the treatment planning and delivery process is key to ensure the optimal benefit from IMRT and IGRT. Uncertainties may stem from a range of sources, including target definition and outlining, mechanical uncertainties in imaging and delivery systems, setup errors and inter- and intrafraction target shape variations. Following a comprehensive literature review, the focus of this key question was to examine setup variability and target volume shape variation. A thorough overview of the uncertainties is provided in a separate publication by Mantello et al [145].

Systematic and random errors in treatment setup, along with variations in target volume shape, were observed both between and within treatment fractions (interfraction and intrafraction) [34,35,146–172]. Despite the implementation of (online) IGRT, geometric variations in the CTV, particularly in the mesorectum, remained a significant and non-negligible source of interfraction and intrafraction uncertainty [35,147,148,150,151,153–159,162,163,166,168,170,172]. For the mesorectum, greater displacement was observed on the anterior surface of the upper half compared to the lower half; and conversely, the posterior surface exhibited more pronounced movement in the lower half compared to the upper half [34,147,148,150,151,162,163,169]. For the primary GTV, significant interfraction motion was also reported [148,150,155,158,166,170]. Position variation of individual involved lymph nodes appears to be strongly dependent on the position and specific lymph node compartment [173].

Non-negligible intrafractional organ motion was reported for both primary tumour and involved nodes, with additional increases observed for session durations exceeding 15 min [154,156,170].

As discussed in KQ 1, the use of a prone position with a bellyboard resulted in increased reported systematic and random setup errors [20,22,29,32].

In conclusion, systematic and random errors in setup and target volume shape variation are substantial and should be accounted for in the target volume margins. Setup errors can be effectively corrected using daily 2D or 3D IGRT, while target volume shape variations remain a challenge, emphasizing the importance of daily volumetric imaging (CBCT or MVCT) or adaptive workflows, to assess daily anatomical changes [174,175]. As different systematic and random errors were observed across the CTV sub-regions (GTVp, GTVn, mesorectum, and elective lymph node regions), the required margins should be defined separately (and possibly anisotropic) for each sub-region, reflecting their distinct motion patterns. For the sake of completeness, when calculating PTV margins, *all* errors in the treatment planning and delivery chain should be considered, not just those discussed here [174,176,177].

KQ 14) What is the optimal IGRT protocol to verify dose delivery?

An optimal IGRT protocol is closely associated with the expected interfractional and intrafractional positional variability of the target volume and surrounding OAR. A large number of studies have investigated interfractional and intrafractional uncertainties in patients with rectal cancer and especially interfraction target volume shape changes are large, see KQ13 and supporting paper Mantello et al [145]. Various factors have been identified that influence these changes, see KQ1 and KQ2. An additional critical factor is the choice of CTV to PTV margins and the underlying definition of the CTV. Based on these considerations, expert consensus (unanimously) is to always use daily volumetric imaging.

Decision making tools (e.g. traffic light protocols) should be defined (expert consensus, unanimously) in a multi-disciplinary setting to support (RTT-led) image evaluation and decision making in a daily volumetric imaging setting [11,174,178–180], see also Flowchart, Fig. 1 and the supporting images in Fig. 2. In these protocols, thresholds are typically defined for setup and anatomical changes, to ensure target coverage while minimizing dose to the surrounding healthy tissues.

Discussion

These ESTRO guidelines provide comprehensive recommendations for all technical aspects of radiotherapy planning and delivery with IMRT and IGRT for rectal cancer. With the widespread uptake of IMRT for rectal cancer [14], this guidance is expected to support broad clinical use.

However, in the process of synthesizing these guidelines, several key gaps in the literature became evident. When there was insufficient literature available, expert consensus was reached through voting. The panel was designed to be representative, including 2 RTTs, 2 MPEs, and 3 ROs. The members were a mix of academic and local experience and were geographically distributed across Europe. The small size of the group may have impacted on the outcome.

For imaging for treatment planning, it is currently unclear which strategies for bladder and rectal filling will optimally ensure consistent anatomy during treatment delivery. While most departments implement some form of patient preparation, high-quality data on this topic remains scarce [181].

For treatment planning, there is an overall lack of comprehensive dose volume response data for OAR in rectal cancer. This is particularly the case for modern treatment techniques (IMRT/VMAT) and for SCRT. Given the dependence of effective optimization of IMRT/VMAT treatment planning on this information [9], there is an obvious need for further research. Simply implementing IMRT may not be sufficient, if it is not clear which normal tissues to spare and how. This was illustrated by a recent paper from the RAPIDO trial, which compared toxicity in patients treated with and without IMRT, and found no benefit of the latter [9]. Despite the non-randomised nature of the comparison, and

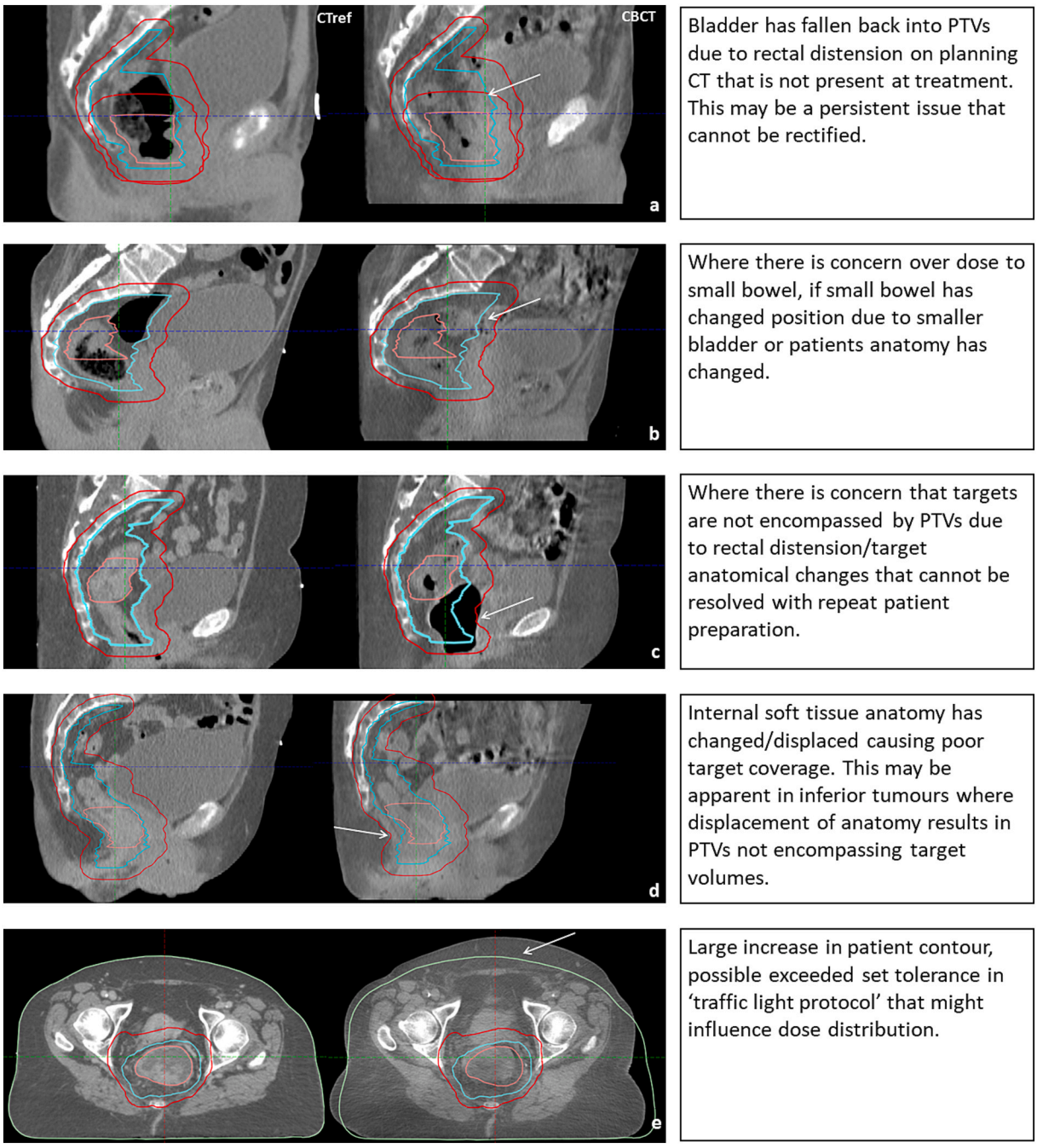

Fig. 2.

the risk of centre-bias, these data provide a sobering reminder that newer techniques are not always a guarantee of improved outcomes. The evidence is even more lacking for optimisation of radiotherapy in emerging indications and settings, such as changing multimodality regimens like TNT or the combination with immuno- or targeted therapy. Dose-response and dose-volume effects may be impacted by such combination treatments. Other emerging scenarios (such as definitive radiotherapy for organ preservation) have seen almost no evaluation of normal tissue toxicity; and consequently, it is unclear which OAR should be delineated, optimised and evaluated in these settings [112,113]. Rectal wall, for instance, may potentially need to be considered as an OAR in the context of organ preservation where the rectum is not removed, but with no published data to date. There is a lack of data on normal tissue dose response for late toxicity for patients treated at higher dose levels (>55 Gy), especially where this has been part of an organ preservation strategy. Additionally, there is a lack of patient reported outcome data, with only a single study assessing patient-reported acute gastrointestinal symptoms [182].

A number of important topics were excluded from the current guideline from the outset. This included CTV and GTV definition: The former has already been covered by an ESTRO guideline [15], while the latter will be covered in a separate guideline under development by the ESTRO Lower GI guideline committee. As a direct consequence, the use of different imaging modalities for target volume definition, and other general radiological questions, such as MR sequencing for the MRI-only workflow (KQ12), were not covered here either. Also related to target volume definition, we deliberately choose not to provide simple recommendations for PTV margins, as optimal margins vary significantly depending on local departmental workflows. A comprehensive review of errors related to setup and target volume deformation can be found in a

separate publication and local margin calculations can be supported by these data [145].

Online volumetric imaging is strongly recommended, as it can identify patients where the margins used do not suffice and may require plan adaptation [11,176–180]. New tools have enabled other forms of adaptive radiotherapy [183,184 185–188]. The most promising technique is online adaptive radiotherapy [189–193]. This approach may be particularly advantageous for highly deformable targets, such as in rectal cancer, and is especially relevant in the context of dose escalation for organ preservation. Although promising in reducing treated volumes, these techniques were not included in this guideline due to limited accessibility and because clinical studies are still awaited to confirm this (e.g., NCT05883800, NCT06854679, NCT05108428).

Conclusion

We have provided guidelines for the clinical development and implementation of IMRT and IGRT. The overall level of evidence was often low and/or derived from expert consensus, underscoring the need for further research. Well-designed prospective clinical trials are essential to bridge existing knowledge gaps and enhance the quality of evidence regarding the application of IMRT and IGRT in the treatment of rectal cancer.

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CRediT authorship contribution statement

Rianne de Jong: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Robin De Roover:** Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Lynsey Devlin:** Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Cihan Gani:** Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Giovanna Mantello:** Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Daniel Portik:** Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Ane Appelt:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Appendix A. Supplementary material

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Rianne de Jong[a,*], Robin De Roover[b], Lynsey Devlin[c,d], Cihan Gani[e], Giovanna Mantello[f], Daniel Portik[g,h], Ane Appelt[i,j]

[a] *Department of Radiation Oncology, Leiden University Medical Centre, Leiden, the Netherlands*
[b] *Department of Radiation Oncology, University Hospitals Leuven, Leuven, Belgium*
[c] *Department of Radiotherapy, The Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom*
[d] *CRUK RadNet Glasgow, University of Glasgow, Glasgow, United Kingdom*
[e] *Department of Radiation Oncology, University Hospital and Medical Faculty Tübingen, Eberhard Karls University Tübingen, Tübingen, Germany*
[f] *Radiotherapy Department, Azienda Ospedaliero Universitaria delle Marche, 60126 Ancona, Italy*
[g] *Department of Radiation Oncology (Maastro), GROW Research Institute for Oncology and Reproduction, Maastricht University Medical Centre+, Maastricht, the Netherlands*
[h] *European Organisation for Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium*
[i] *Leeds Institute of Medical Research, University of Leeds, Leeds, United Kingdom*
[j] *Department of Oncology, Section of Radiotherapy, Rigshospitalet - Technical University Hospital of Greater Copenhagen, Copenhagen, Denmark*

[*] Corresponding author at: Department of Radiation Oncology, Leiden University Medical Centre, Postbus 9600 | 2300 RC Leiden.
E-mail address: m.a.j.de_jong@lumc.nl (R. de Jong).