Clinical and Translational Radiation Oncology 58 (2026) 101131

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Practice Guidelines

ESTRO consensus guidelines on GTV delineation and dose-escalation in rectal cancer

1. Introduction

In recent years, the treatment paradigm for rectal cancer (RC) has increasingly shifted toward dose intensification strategies, aiming to enhance complete response (CR) rates [1,2]. Achieving CR is clinically meaningful, as it significantly increases the likelihood of organ preservation and functional sphincter-sparing outcomes—particularly critical in younger patients, for whom long-term quality of life (QoL) and avoidance of permanent colostomy are paramount [3,4] and older patients with comorbidities rendering them not suitable for surgery [5].

Organ preservation represents a major evolution in the management of RC, with nonoperative approaches such as Watch-and-Wait (WW) strategies and local excision (LE) gaining prominence [2]. These approaches are supported by a growing body of clinical trials dedicated to nonoperative management (NOM), reflecting a broader movement toward personalized and function-preserving therapies [4,6,7].

Treatment intensification, particularly through radiotherapy (RT) dose escalation, is a key modality to increase complete clinical response (cCR) rates. Meta-analyses and large cohort studies have consistently demonstrated that dose escalation can improve oncologic outcomes in this context [8–10]. However, despite mounting evidence supporting this approach, there is currently no consensus on how to define the gross tumor volume (GTV) when a radiation dose escalation is planned.

To bridge this gap, we convened an international panel of RC experts with extensive clinical and academic experience, including recognized proficiency in organ-preservation strategies. This initiative was conducted within the framework of the 'Guidelines Sub-Group on Lower GI' of ESTRO (European Society for Radiotherapy and Oncology).

Using a structured Delphi methodology, we collected and synthesized expert contributions to develop, to our knowledge, the first Consensus Statement on GTV delineation for RC, with particular emphasis on dose-escalated RT aimed at organ preservation. This technical guideline provides consensus-based recommendations on optimal imaging modalities, dose specifications and GTV definition, with the overarching goal of promoting standardization and improving treatment outcomes for patients with RC.

2. Materials and methods

A comprehensive search of PubMed/MEDLINE, the Cochrane Library, and Google Scholar was conducted to identify studies reporting on the contouring of GTV, clinical target volume (CTV), and planning target volume (PTV), RT dosing, indications for and delivery strategies of boost irradiation, and outcomes from dose-escalation trials in rectal cancer, covering all publications from December 2003 up to April 2023 (Supplementary Table S1. Data extraction from eligible retrospective, prospective, and randomized studies was independently performed by two reviewers (A.R. and G.C.). Based on the selected articles, statements were identified and subsequently organized into thematic domains.

Consensus recommendations were developed by a multidisciplinary panel comprising clinical and radiation oncologists, medical oncologists, a pathologist, radiologists with expertise in RC, and a medical physicist, using the Delphi methodology. Panelists recorded their votes via Google Forms (Google LLC; https://docs.google.com/forms/), with additional supporting materials shared by For each statement, the degree of agreement was evaluated using three response options: *agree; partially agree* (in which case explanatory comments were required); or *disagree*.

A minimum agreement threshold of 70% was required to establish consensus on each item. Items that did not reach this threshold in the first round were reconsidered in the second round. If the level of agreement remained below 70% after the second round, the statement was excluded from the final set.

In addition, three illustrative clinical cases (Supplementary Material 1) hosted on the Falcon (https://estro.educase.com/) platform were selected. The first case involves a low rectal tumor with positive extramesorectal lymph nodes, the second a low rectal tumor, and the third a high-risk locally advanced tumor associated with positive extramesorectal lymph nodes.

Independent delineations by the expert panel members were compared to determine consistency. A quantitative assessment of interobserver variability was performed using Dice similarity coefficient, Hausdorff distance, Jaccard index, as well as absolute contoured volumes. The Dice and Jaccard coefficients quantify the spatial overlap between manual and automatic segmentations, with values closer to 1 indicating a higher degree of agreement. The Hausdorff distance measures the maximum boundary deviation between the two segmentations; lower values indicate a closer geometric correspondence [11]. For each metric, results are reported as mean, standard deviation, and range (minimum–maximum).

At the end of this process, all proposed contours were reviewed and a ground truth delineation was established. Based on the initial contouring submissions and the subsequent modifications discussed and implemented by the expert panel, a final consensus structure was generated. This definitive delineation was then established as the ground truth and made available to Falcon members for training purposes. (https://estro.educase.com/index.php/component/educase/?view=case&action=categories&cat_id=423&Itemid=163).

https://doi.org/10.1016/j.ctro.2026.101131
Received 13 February 2026; Accepted 16 February 2026
Available online 20 February 2026
2405-6308/© 2026 The Authors. Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

3. Results

3.1. Literature search and review

A total of 736 publications were initially retrieved through the literature search. After removing duplicates and screening titles and abstracts, 360 articles were selected for full-text evaluation. Following the exclusion of studies not written in English, those without accessible full text, and those not addressing the specific topic (e.g., lacking information on GTV or CTV contouring), 19 studies were ultimately included as relevant to the scope of the present review (Supplementary Fig. S1). For each included study, data were extracted regarding the boost indication, technology employed for dose boost delivery, prescribed dose and fractionation, study outcomes, and methods of target definition (GTV, CTV) according to the diagnostic imaging modality used (Supplementary Table S1).

Based on the findings of the literature search described above, 5 specific domains were identified: 1) *Indication for dose escalation in rectal cancer* 2) *Advanced approaches to dose escalation* 3) *GTV definition 4) GTV-CTV delineation 5) GTV evaluation during RT.*

From these domains, a total of 24 statements were formulated. These statements were subsequently submitted to the expert panel for evaluation within a Delphi survey.

3.2. Consensus procedures and Delphi rounds

The statements used in the first and second Delphi rounds on the 5 selected domains, together with the corresponding answers, are provided (Supplementary Table S2 and S3).

Fifteen experts were invited to participate in the first Delphi round (R1). Eleven out of 15 (73.3%) completed the R1 survey. Among the 24 statements, 18 (75%) reached the predefined consensus threshold of at least 70% agreement and were therefore considered as agreed upon (Supplementary Table S2). The remaining 6 statements (25%) failed to achieve the required threshold in the first round and were thus included in the second round for re-evaluation. Comments provided on statements, including explanatory notes, were collected and incorporated into the subsequent round.

During the second Delphi round (R2), the 6 statements that failed to achieve consensus in the first round (R1) were re-evaluated. Given that two questions dealt with overlapping aspects of GTV of primary tumor (GTVp) to CTV of primary tumor (CTVp) margin definition in relation to risk stratification, they were merged into a single item, resulting in 5 statements being resubmitted for voting. All 15 experts participated in R2, with 3 statements receiving responses from 15 panelists and 2 statements from 14 panelists. Among the 5 statements of R2, 2 (40%) achieved the predefined consensus threshold of $\geq$ 70% agreement, while 3 statements (60.0%) did not reach consensus (Supplementary Table S3). In addition, based on panelists' comments, a total of 10 statements—including those without consensus and those that had already reached agreement—were rephrased for improved clarity. Table 1 shows the 20 statements developed overall.

3.3. Falcon clinical cases delineation

The 3 selected cases represent RC with distinct clinical presentations. Fig. 1 illustrates the contours generated by the participating panellists. For each case, both GTVp and, for Case 1 only, nodal GTV (GTVn) volumes were considered.

Across all three cases, the mean Dice coefficient was 0,83 ± 0,09 (range 0,7–1), the mean Hausdorff distance was 7,98 ± 4,25 (range 1–15,83), and the mean Jaccard coefficient was 0,71 ± 0,14 (range 0,47–1).

With respect to volumes, the mean GTVp volume for Case 1 was 41,64 ± 8,99 cm^3 (range 26,14–56,33), for Case 2 14,18 ± 2,12 cm^3 (range 11,82–18), and for Case 3 94,03 ± 12,03 cm^3 (range

Table 1
The 20 statements developed for dose escalation in rectal cancer: definition and delineation of the gross tumor volume (GTV).

Domain	Statements	Agreement (%)
Indication for dose escalation in rectal cancer	1. Dose escalation was defined as any dose greater than 54 Gray.	90,9
	2. Dose escalation leads to more downstaging and more nCR/cCR.	72,7
	3. Dose escalation is especially indicated for tumors located at the mid-lower rectum (near the anal verge) to avoid surgery.	90,9
	4. Dose escalation is advised in patients with multiple co-morbidities and/or in patients who are not considered to be suitable for surgery, with the goal of pursuing organ-preservation protocols.	90,9
Advanced approaches to dose escalation	5. There is no strict guidance on techniques and modalities of boost administration. It can be administered either sequentially or simultaneously. The latter is preferred in the setting of dose escalation.	90,9
	6. Dose escalation strategies to at least 60–62 Gy may be considered if the tumour is within 6 cm of the anal verge. In such cases, endoluminal approaches like CXB or HDR-BT, as well as advanced techniques, such as M-RIgRT, should be considered, based on expertise and availability.	85,7
	7. CXB and HDR-BT are two alternatives to dose intensification on the GTV when a conservative approach is desired.	100
	8. Studies in rectal cancer using proton beam therapy have shown promising results for sparing OARs, but further research is needed to validate its use.	90,9
GTV definition	9. GTV is represented by primary tumour (GTVp) and may include lymph node disease (GTVn) and tumoral deposits (Nc).	70
	10. MRI is mandatory to define GTV boost volume. It is the gold standard technique for both primary staging and restaging of rectal cancer, as well as for complete assessment of all compartments and lymph nodes.	90,9
	11. Endorectal filling in diagnostic rectal MRI is not recommended.	100
	12. In an organ preservation approach, in order to boost positive nodes, both morphological and dimensional criteria should be considered in the radiological evaluation of suspicious mesorectal lymph nodes.	100
	13. DWI MRI and DCE MRI are not recommended to detect involved lymph nodes.	90,9
	14. 18F-FDG PET/CT may be helpful as a problem solver in the case of (large) equivocal nodes on MRI.	80
	15. There is no evidence that 18F-FDG PET/TC provides a significant contribution to the definition of a biological target volume for radiotherapy treatment planning.	78,6
GTV-CTV delineation	16. For the delineation of the GTV, the use of the MR co-registered with the simulation CT is recommended.	72,7
	17. A 0.5 cm margin from GTVn to CTVn may be considered.	81,8
GTV evaluation during RT	18. Rectal cancer patients undergoing chemoradiation experience a reduction in tumor volume, with the	90,9

(*continued on next page*)

Table 1 (*continued*)

Domain	Statements	Agreement (%)
	most substantial decrease observed in the first half of treatment.	
	19. The intermediate MRI (at the 10th treatment fraction), acquired both by MR Linac and diagnostic MRI, provides valuable information on tumor volume reduction and treatment response and may allow clinicians to adapt strategies and make informed decisions during the course of therapy.	81,8
	20. The end of the second week of treatment or reaching a dose of $BED_{\alpha/\beta=5} = 25$ Gy represents a potential point during radiation therapy to apply dose escalating strategies in poor responders.	81,8

18F-FDG PET/TC: 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography; BED: biologically effective dose; cCR: clinical complete response; nCR: near complete response; CXB: Contact X-ray brachytherapy; DCE: dynamic contrast-enhanced; DWI: Diffusion-weighted imaging; HDR-BT: high-dose-rate brachytherapy; nCR: near complete response; OARs: organs at risk; MRI: Magnetic resonance imaging; MRIgRT: MR guided radiation therapy;

74,54–112,85). In addition, the GTVn volume for Case 1 was 0,51 ± 0,23 cm^3 (range 0,28–0,89). These results indicate a noticeable degree of variability across observers. More detailed values for each case and observer are available in Supplementary Table S4.

3.4. Indication for dose escalation in rectal cancer

Statement 1. Dose escalation was defined as any dose greater than 54 Gray. (Agreement: 90,9%).

Dose-response analyses have reported increased response rates with increasing RT dose. Appelt et al. reported dose–response analyses indicating that doses as high as 92 Gy (equivalent dose in 2 Gy per fraction [EQD2]) are needed to achieve a complete histopathologic tumor regression (TRG 1) in 50% of patients, and doses of 72 Gy or higher are needed to achieve a major tumour response (TRG 1–2) in 50% of cT3–4 rectal tumours [12].

Radiation dose escalation in the settting of neoadjuvant treatment of RC with planned radical TME surgery remains a matter of debate, as supporting evidence is limited. While substantial data exist regarding prolonged intervals to surgery, includingthe use of TNT, most studies addressing radiation dose intensification in the neoadjuvant setting with external beam radiotherapy (EBRT) are retrospective, often with small sample sizes, and only a few prospective trials have been reported [13–17].

Nevertheless, the available evidence supports a strong dose–response effect in rectal adenocarcinoma. Tumour regression is enhanced within the 50.4–70.0 Gy dose range, findings corroborated by WW strategies that typically employ doses ≥ 54 Gy [12,18,19].

Efforts to improve cCR rates through radiation dose escalation and intensified neoadjuvant regimens have shown encouraging results [1,3]. Several studies report higher cCR rates with these approaches; however, variability in response, likely reflecting differences in patient selection, and increased risk of treatment-related toxicity, remains a significant challenges [2,20].

For example, Appelt et al. reported a 78% cCR rate with high-dose RT (60 Gy plus brachytherapy [BT]), though with an increased risk of long-term toxicity [3]. Similarly, Habr-Gama observed that dose escalation (54 Gy combined with neoadjuvant chemotherapy (CHT) consisting of 5-fluorouracil/leucovorin delivered in six cycles every 21 days) increased cCR rates to 57% [21]. A subsequent study from the same group comparing standard chemoradiotherapy (CRT) (50.4 Gy with two cycles of 5-FU–based CHT) with extended CRT (54 Gy with six cycles of 5-FU–based CHT) confirmed the benefit of slightly higher RT dose and adding additional chemotherapy cycles demonstrating significantly higher cCR rates with the escalated regimen (30% vs. 67%) [2]. Taken together, these findings indicate that intensified treatment strategies can improve oncological outcomes, but standardized protocols are still lacking [22].

Statement 2. Dose escalation leads to more downstaging and more nCR/cCR. (Agreement: 72,7%).

Organ preservation strategies are particularly appealing in clinical contexts where Total Mesorectal Excision (TME) might otherwise be required. TME is associated with considerable long-term morbidity: approximately one-third of patients require a permanent colostomy, up to 90% of those undergoing low anterior resection (LAR) experience some degree of Low Anterior Resection Syndrome (LARS), and urinary and sexual dysfunction occur in about 33% and 50% of cases, respectively [23].

Statement 3. Dose escalation is especially indicated for tumors located at the mid-lower rectum (near the anal verge) to avoid surgery. (Agreement: 90,9%).

Organ preservation strategies are increasingly regarded as feasible for carefully selected patients, particularly those refusing surgery or those with tumours located in the lower rectum where abdominoperineal resection (APR) would otherwise necessitate a permanent colostomy [24].

A major limitation of exclusive CRT in early RC remains the risk of residual disease and failure to achieve cCR necessitating additional (major) surgery and, thus, potential overtreatment in cases where upfront CRT would not have been routinely indicated.. CRT treatment intensification in this subgroup may increase the likelihood of achieving cCR and adopting a conservative strategy, but needs to be balanced with the risk and potentially increased morbidity of salvage surgery in case of incomplete response. There are two approaches to the WW strategy:

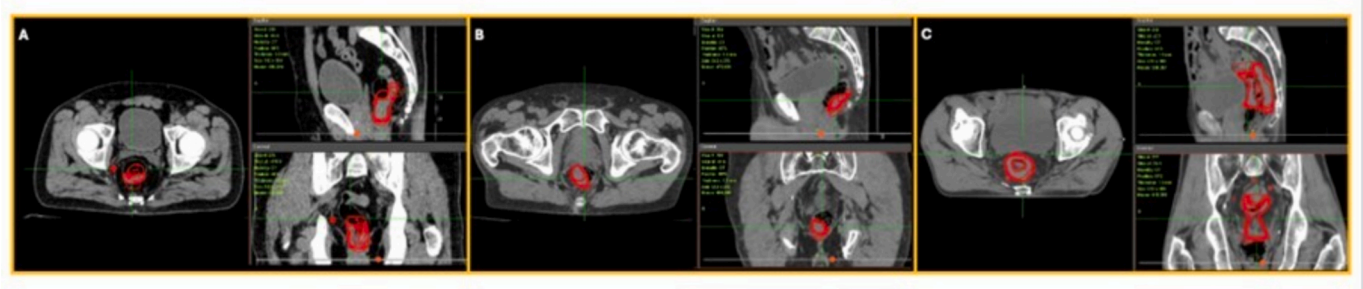

Fig. 1. Contours generated by the panelists on the three representative clinical cases uploaded to the ESTRO FALCON platform. From top to bottom: Case 1 (A), Case 2 (B), and Case 3 (C). For each case, axial, coronal, and sagittal CT simulation slices are shown. The primary tumor volume (GTVp) is delineated in all cases, while the nodal volume (GTVn) is contoured only in Case 1 (A). Observer delineations are displayed in red, overlaid to highlight the degree of overlap and variability across participants. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

opportunistic and intentional. The opportunistic approach takes advantage of achieving cCR in patients undergoing routine preoperative CRT. Whereas in the intentional approach, the main goal of CRT is to avoid surgery. This is achieved by radiation dose escalation, additional CHT after CRT/RT (i.e. total neoadjuvant therapy) or delivering standard or intensified CRT to patients with small cancer, who would not otherwise require preoperative radiation [22,25,26].

Statement 4. Dose escalation is advised in patients with multiple comorbidities and/or in patients who are not considered to be suitable for surgery, with the goal of pursuing organ-preservation protocols. (Agreement: 90,9%).

In recent years, increasing attention has been devoted to balancing curative efficacy with QoL. This has led to growing skepticism regarding the indiscriminate use of surgery in all patients with RC [22,23]. Neoadjuvant therapy can be safely completed in approximately 86% of elderly patients, with R0 resection rates and recurrence outcomes comparable to those observed in younger cohorts [27]. Advanced age alone should not therefore be considered a contraindication to treatment. However, elderly patients often present with greater surgical risks due to comorbidities and reduced cardiopulmonary reserve, raising concerns about the feasibility of radical procedures such as TME [27]. For frail elderly patients who are not candidates for major surgery or CRT, modern RT techniques, including volumetric modulated arc therapy (VMAT), MRI-guided RT (MRIgRT), and endoluminal BT, represent viable non-operative alternatives [28].

High-precision RT with dose escalation is particularly advantageous in this vulnerable population, as it provides durable local tumor control, reduces disease-related complications, and enhances QoL. Conversely, radical surgery in elderly patients carries significant perioperative risk, with mortality rates reaching up to 36.8% in specific subgroups and even higher among the frailest patients [29]. In this context, NOM has emerged as an important therapeutic strategy, allowing effective local disease control. Recent studies have reported encouraging results with NOM, including a 3-year overall survival rate of 97% in selected elderly patients [30].

3.5. Advanced approach of dose escalation

Statement 5. There is no strict guidance on techniques and modalities of boost administration. It can be administered either sequentially or simultaneously. The latter is preferred in the setting of dose escalation. (Agreement: 90,9%).

There is currently no strict consensus regarding the optimal strategy for EBRT boost delivery in RC dose escalation. Comparative analyses of dosimetry, toxicity, and survival outcomes have reported similar results across different approaches [31]. A recent study of 88 patients treated with neoadjuvant CRT using VMAT showed that the Simultaneous Integrated Boost (SIB) reduced doses to all organs at risk (OARs), except for the bladder and bowel maximum dose and the right femoral head mean dose, when compared to sequential boost [32]. While SIB appears advantageous for dose escalation, sequential boosting retains the benefit of facilitating adaptive treatment modifications [32]. Although tumor regression predominantly occurs during the early phase of CRT and slows thereafter [33], suggesting a potential rationale for sequential strategies, SIB may offer greater flexibility for adaptive planning during treatment.

Statement 6. Dose escalation strategies to at least 60–62 Gy may be considered if the tumour is within 6 cm of the anal verge. In such cases, endoluminal approaches like CXB or HDR-BT, as well as advanced techniques, such as MRIgRT, should be considered, based on expertise and availability. (Agreement: 85,7%).

Beyond EBRT, dose escalation has been explored through endoluminal radiotherapeutic modalities. Endorectal high-dose-rate brachytherapy (HDR-BT) is particularly suitable for small tumors, as it improves dose conformity while sparing adjacent tissues [34]. Contact X-ray brachytherapy (CXB) and HDR-BT have both been evaluated in randomized trials [1,35]. Magnetic resonance image-guided RT has recently emerged as a promising tool to enable adaptive RT (ART) for RC. A prospective phase II trial evaluated high-dose RT (62 Gy in 28 fractions) with CHT and reported that 86% of patients achieved a cCR, with 61% maintaining sustained cCR at 2 years. Overall survival at 30 months was 94.8% with manageable toxicity, demonstrating the feasibility of organ preservation with modern RT [36]. Based on these results, a randomised trial is currently ongoing to compare rectal preservation rates between a 62 Gy boost and standard CRT at 50.4 Gy (NCT04095299) [37]. Additional prospective studies have further confirmed the safety and feasibility of MRIgRT-based dose escalation, up to 60.1 Gy, including tumors in the lower rectum [38–41].

Statement 7. CXB and HDR endoluminal BT are two alternatives to dose intensification on the GTV when a conservative approach is desired. (Agreement: 100%).

In the OPERA [1] trial patients received a CXB boost of 90 Gy in 3 fractions over 4 weeks, delivered before or after EBRT depending on tumor size, while in the MORPHEUS trial [35] the boost arm consists of three weekly HDR endorectal BT boosts (total 30 Gy) following EBRT. In the OPERA trial, most rectal bleeding events in the CXB boost arm were mild (grade 1–2, 63%) and resolved over time, with grade 2–3 proctitis in 13% of patients. In the MORPHEUS trial, acute toxicities were similar between image-guided adaptive radiotherapy (IGAEBT) and standard EBRT, with only 2 patients (10%) in the IGAEBT arm experiencing grade 3 proctitis, both of which resolved with local treatment [1,35]. These approaches demonstrated that dose escalation using BT can be safely delivered after CRT, supporting organ-preservation strategies. For patients achieving a cCR, this may allow safe avoidance of radical surgery while maintaining anorectal function and QoL. However, clinical application remains limited to specialized centers with the necessary expertise and equipment.

Statement 8. Studies in rectal cancer using proton beam therapy have shown promising results for sparing OARs, but further research is needed to validate its use. (Agreement: 90,9%).

Proton beam therapy (PBT) offers the potential to reduce radiation exposure to OARs while preserving tumor coverage. Compared with conventional techniques, PBT significantly decreases the volume of irradiated small bowel at higher doses [42] and reduces irradiation of the bladder and pelvic bone marrow [43,44]. Although data on urinary dysfunction are limited [45], PBT has shown promise in reducing bladder irradiation [44]. Widespread clinical adoption is hindered by cost, limited availability, and the lack of randomized controlled trials. Nevertheless, cost-effectiveness analyses suggest potential long-term benefits, particularly through reduced late toxicity and improved QoL [46,47].

3.6. GTV definition

Statement 9. GTV is represented by primary tumour (GTVp) and may include lymph node disease (GTVn) and tumoral deposits (Nc). (Agreement: 70%).

In the recent studies, GTV is defined by the primary tumour (GTVp) and, in some cases, by positive lymph nodes (GTVn) and tumoral deposits (nC) (Supplementary Table S1) [15,48–53].

Statement 10. Magnetic resonance imaging (MRI) is mandatory to define GTV boost volume. It is the gold standard technique for both primary staging and restaging of rectal cancer, as well as for complete assessment of all compartments and lymph nodes. (Agreement: 90,9%).

For defining the boost GTV, MRI is required. A minimum MRI protocol should include 2D T2-weighted sequences acquired in three planes (axial, sagittal, and coronal). Coronal images should be angulated parallel to the tumor, and an axial diffusion-weighted sequence (with at least a high b-value of $\geq$ b800) should also be included. Diffusion-weighted imaging (DWI) should be assessed visually on both DWI and apparent diffusion coefficient (ADC) maps, while quantitative ADC measurements are not routinely recommended. DWI-MRI should be

performed routinely, especially for restaging to evaluate tumor response (yT stage) after CRT. Conversely, fat-suppressed T1-weighted sequences (non-enhanced and contrast-enhanced) and dynamic contrast-enhanced (DCE) sequences are not routinely advised [54,55].

Image acquisition should be tailored to the rectal tumor axis: oblique high-spatial resolution transverse T2-weighted sequences, should be angulated perpendicular to the tumor. For distal tumours, a coronal sequence aligned with the anal canal is recommended to assess the tumor–sphincter relationship. Slice thickness should be $\leq$ 3 mm [55]. For RT planning, the clean, non-angulated axial T2 sequence may provide valuable information.

Statement 11. Endorectal filling in diagnostic rectal MRI is not recommended. (Agreement: 100%).

International guidelines recommend the use of a micro-enema to reduce the amount of luminal gas [55]. Endorectal filling in rectal MRI is not recommended, because distention of the rectal wall may interfere with interpretation of the distance between the tumour and the mesorectal fascia. Another potential disadvantage of rectal gel filling is that the high T2 signal of the gel may cause T2 shine through effects on DWI.

Statement 12. In an organ preservation approach, in order to boost positive nodes, both morphological and dimensional criteria should be considered in the radiological evaluation of suspicious mesorectal lymph nodes. (Agreement: 100%).

Accurate reporting of (lateral) lymph nodes requires high resolution T2-weighted images (slice thickness $\leq$ 3 mm, 23 plane resolution of $\pm$ 0.6 $\times$ 0.6 mm). At least one sequence with a large field of view (FOV) should cover the craniocaudal plane from the sacral promontory to the anal canal, enabling evaluation of lateral compartments and all relevant nodal stations [56]. The Dutch Criteria, endorsed by ESGAR and the Society of Abdominal Radiology's Colorectal and Anal Cancer Disease-Focused Panel, should be applied to determine which pathological nodes require a boost. According to these criteria, suspicious mesorectal, superior rectal, and inferior mesenteric nodes include: (i) short-axis diameter $\geq$ 9 mm; (ii) diameter 5–8 mm with $\geq$ 2 suspicious features (irregular borders, heterogeneous signal, round shape); (iii) diameter $<$ 5 mm with $\geq$ 3 suspicious features; or (iv) mucinous nodes of any size [55].

More recently, the Lateral Node Consortium has emphasized nodal size over morphology in predicting risk. Specifically, lateral pelvic nodes (internal iliac and obturator) $\geq$ 7 mm are associated with increased risk of local recurrence following CRT and LAR in cT3/4 tumors $<$ 8 cm from the anal verge. Therefore, all visible lateral nodes should be reported, including location and short-axis diameter [56,57].

Statement 13. DWI MRI, DCE MRI are not recommended to detect involved lymph node. (Agreement: 90,9%).

DWI-MRI may improve lymph node visibility, but highlights both positive and negative nodes and quantitative ADC measurements have limited discriminatory value [56]. While DCE-MRI has shown promising results, no consensus currently supports its routine clinical use in RC nodal assessment [55,58].

Statement 14. 18F-FDG PET/CT may be helpful as a problem solver in the case of (large) equivocal nodes on MRI. (Agreement: 80%).

18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (18F-FDG PET/CT) is not routinely advised for RC staging and appears to have limited value for assessment of smaller nodes considering these may fall under the detection limit and/or are obscured by uptake from the tumor or bladder. Therefore, 18F-FDG PET/CT may serve as a problem-solving tool for large or equivocal nodes on MRI [56].

Statement 15. There is no evidence that 18F-FDG PET/CT provides a significant contribution to the definition of a biological target volume for radiotherapy treatment planning (Agreement: 78,6%).

Although 18F-FDG PET/CT has proven useful for RT planning in other tumor types [59], it is not routinely recommended for rectal cancer.

3.7. GTV-CTV delineation

Statement 16. For the delineation of the GTV, the use of the MR co-registered with the simulation CT is recommended. (Agreement: 72,7%).

Image fusion with the planning CT scan is strongly recommended [60]. For target delineation, a preferably non-angulated MRI should be used to ensure reliable co-registration with the planning CT. However, this approach is limited by internal organ motion between the two scans, which reduces spatial accuracy. To overcome this issue, some institutions have adopted MR-only workflows, where dose distribution is calculated directly on MR images after assigning Hounsfield unit values through artificial intelligence algorithms. A practical strategy to improve consistency would be to acquire both diagnostic MRI and CT simulation under the same rectal and bladder filling conditions, thereby maximizing the accuracy of GTV definition on CT. Within this context, synthetic CT (sCT) has emerged as a promising tool, particularly in MR-only workflows. By providing improved soft-tissue contrast, more accurate dose calculations, and avoiding MRI–CT registration errors, sCT has the potential to enhance delineation of lateral nodal compartments and reduce inter-observer variability. Nevertheless, current evidence is insufficient to confirm these benefits, and further research is required to determine whether delineating directly on the planning MRI improves accuracy and reproducibility [55]. Interestingly, although endorectal ultrasound gel is not recommended for diagnostic MRI, its use has been shown to improve inter-observer concordance in MRI-based rectal tumor delineation. This suggests a possible role in future dose-escalation strategies [61].

Statement 17. A 0.5 cm margin from GTVn to CTVn may be considered. (Agreement: 81,8%).

When considering nodal target volumes, RT dose escalation may represent an alternative to surgery for patients with positive lateral pelvic lymph nodes. Reported GTVn-to-CTVn expansions range from 0 cm [48,62] to 0.5 cm [52] (Table 2).

3.8. GTV evaluation during RT

Statement 18. Rectal cancer patients undergoing chemoradiation experience a reduction in tumor volume, with the most substantial decrease observed in the first half of treatment. (Agreement: 90,9%).

Tumor shrinkage during preoperative CRT adds another layer of complexity. Van den Begin et al. [33] showed that rectal tumors shrink rapidly from the first treatment week, with residual volumes of 46.3% at the end of CRT and 32.4% at surgery. The shrinkage rate was initially high (26% per week), slowing progressively in the later treatment phases (7% per week in the final two CRT weeks and 1.3% per week in the five weeks preceding surgery). These kinetics may help identify early non-responders, support ART strategy, and guide WW strategies.

Statement 19. The intermediate MRI, acquired both by MR Linac and diagnostic MRI, provides valuable information on tumor volume reduction and treatment response, may allow clinicians to adapt strategies and make informed decisions during the course of therapy. (Agreement: 81,8%).

MRI has also been explored as a tool for early response prediction. DWI represents another promising avenue. Kim et al. [63]demonstrated the superior prognostic value of early tumor volume reduction, while Lambrecht highlighted the role of pre-treatment ADC values and their dynamic changes during CRT in predicting pathological response [64].

Taken together, these findings reinforce the rationale for integrating advanced MRI techniques into RT workflows. Serial imaging before, during, and after CRT not only refines target delineation but also enables response-adapted treatment strategies, supporting individualized therapy and the potential for dose escalation in selected patients [63,64].

Statement 20. The end of the second week of treatment or reaching a dose of BED$\alpha/\beta = 5 = 25$ Gy represents a potential point during radiation therapy to apply dose escalating strategies in poor responders. (Agreement: 81,8%).

Palmisano et al. [65] demonstrated that tumor volume assessed after nine CRT fractions (20.7 Gy) could stratify patients into complete,

Table 2
Panelist-derived definitions of GTVp (gross tumor volume–primary tumor), GTVn (gross tumor volume–nodes), and the corresponding CTVp and CTVn (clinical target volumes primary tumor and nodal), with supporting notes. Recommended structure naming follows ICRU recommendations and AAPM TG-263 [71].

Name of volume	Abbreviation	Definition	Notes
GTV primary	GTVp	Macroscopic primary tumor	MRI is mandatory and endorectal filling is not recommended. MRI co-registered with the simulation CT is recommended. The role of 18F-FDG PET/CT has not been clearly established.
GTV node	GTVn	Pathological lymph nodes according to size and morphologic features.	MRI is mandatory. GTVn includes lymph node disease (GTVn) and tumoral deposits (Nc).
CTV primary	CTVp	The volume that might contain significant microscopic subclinical disease.	The range of the margin varies from 0 to 2 cm. In some cases, CTVp is defined as primary tumor plus associated mesorectum
CTV node	CTVn		A 0.5 cm margin from GTVn to CTVn may be considered.

partial, and non-responders using both absolute volume (Vmid) and its variation (ΔVmid). Fiorino et al. [66] developed the Early Regression Index-Tumor Control Probability (ERI-TCP), an MRI-based predictive model of response to neoadjuvant CRT, which achieved high accuracy (AUC = 0.81/0.75 for pCR/cCR, $p < 0.0005$) with strong sensitivity and negative predictive value. Building on these insights, a phase II trial tested an MR-guided adaptive boost up to 60.1 Gy for ERI-TCP–identified non-responders at the 10th treatment session, with the aim of increasing complete response rates. Interim results confirmed the safety and feasibility of this adaptive strategy [38].

4. Discussion and future perspectives

The Delphi process enabled the panel to reach consensus on the definition and delineation of GTV for both GTVp and GTVn in the context of dose escalation for rectal cancer. Dose escalation was defined as any RT dose above 54 Gy, with particular relevance for tumors located in the mid-to-lower rectum, where conventional surgery would otherwise result in a permanent stoma or significant functional morbidity. In these patients, RT intensification offers a realistic opportunity for organ preservation, a goal that has become increasingly central in modern rectal cancer management. For GTVp the panel's recommendations are strongly supported by current evidence. Data indicate that, particularly in low, non-operable cancers, a dose of at least 54–60 Gy is required to achieve clinically meaningful rates of complete response [12,18,21]. Several techniques — including CXB, HDR endorectal BT, and MRI-guided adaptive RT — have further demonstrated the ability to increase tumor regression and sustain long-term organ preservation [1,34,35,38,39]. These findings are echoed in the 2025 ESMO guidelines, which explicitly recognize endorectal BT after standard CRT as a validated dose escalation strategy in selected early cT2–cT3 tumors < 5 cm, when an non-operative approach is pursued [67].

Conversely, the situation is less clear for GTVn. No consensus was achieved regarding GTVn, reflecting the absence of prospective evidence to support nodal dose escalation and the persistent uncertainty surrounding its potential benefits. The panel agreed that only large multicenter databases and prospective trials will be able to clarify whether this strategy could improve outcomes without compromising safety.

Consistently, the 2025 ESMO guidelines emphasize both the lack of supporting evidence for nodal dose intensification and the inherent limitations of MRI-based nodal staging, thereby reinforcing the need for prospective validation before such an approach can be incorporated into clinical practice [67].

Imaging emerged as another important area of convergence. MRI was confirmed as the gold standard for GTV definition, both at staging and restaging, in line with ESGAR and other international guidelines [55]. In contrast, 18F-FDG PET/CT was judged not to contribute meaningfully to either GTV delineation or treatment response assessment. Its use should therefore remain confined to problem-solving in cases of equivocal MRI findings. This position is in line with the 2025 ESMO guidelines, which do not include 18F-FDG PET/CT in the standard diagnostic or treatment planning workflow for localized rectal cancer [67].

Although there is general agreement on the use of imaging modalities, the optimal margin from GTVp to CTVp remains an unsettled issue. Reported margins vary widely, from 0 cm [49–53,60] to 2 cm [52,53] (Table1).Across studies, a shared principle is that diagnostic imaging must be integrated with CT simulation to ensure accurate target definition.

Some groups defined CTVp as the GTVp, plus a 2 cm cranio-caudal margin along the rectal circumference [68], whereas others included the entire mesorectum within the CTVp [48,69,70].

Looking ahead, several research directions appear critical. These include the prospective evaluation of dose intensification to nodal targets; the development of imaging- and risk-adapted approaches to GTV–CTV margin definition, and the integration of functional imaging — particularly diffusion-weighted imaging — for early response prediction and adaptive treatment individualization. Collectively, these directions reflect the broader movement toward personalized treatment, in which radiation dose, margins, and delivery technique are tailored to tumor biology and early indicators of response. In this evolving landscape, novel technologies — including BT, MRIgRT, and PBT — represent promising tools to refine dose escalation strategies, with the aim of maximizing tumor control while minimizing toxicity and preserving long-term function.

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.

Prof Gambacorta reports personal fees from GSK and MSD, outside the submitted work. All other authors report no conflict of interest.

Acknowledgements

The authors would like to acknowledge Prof. Barbaro, Prof. Vendrely, and Prof. Rödel for their critical review of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2026.101131.

References

[1] Gerard J-P, Barbet N, Schiappa R, Magné N, Martel I, Mineur L, et al. Neoadjuvant chemoradiotherapy with radiation dose escalation with contact x-ray brachytherapy boost or external beam radiotherapy boost for organ preservation in early cT2-cT3 rectal adenocarcinoma (OPERA): a phase 3, randomised controlled trial. Lancet Gastroenterol Hepatol 2023;8:356–67. https://doi.org/10.1016/S2468-1253(22)00392-2.

[2] Habr-Gama A, São Julião GP, Vailati BB, Sabbaga J, Aguilar PB, Fernandez LM, et al. Organ Preservation in cT2N0 Rectal Cancer after Neoadjuvant Chemoradiation Therapy: the Impact of Radiation Therapy Dose-escalation and consolidation Chemotherapy. Ann Surg 2019;269:102–7. https://doi.org/10.1097/SLA.0000000000002447.
[3] Appelt AL, Pløen J, Harling H, Jensen FS, Jensen LH, Jørgensen JCR, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol 2015;16:919–27. https://doi.org/10.1016/S1470-2045(15)00120-5.
[4] Rullier E, Rouanet P, Tuech J-J, Valverde A, Lelong B, Rivoire M, et al. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. Lancet 2017;390:469–79. https://doi.org/10.1016/S0140-6736(17)31056-5.
[5] Myint AS, Gérard JP. Role of radiotherapy in the treatment of rectal cancer in older patients. Eur J Surg Oncol 2020;46:349–57. https://doi.org/10.1016/j.ejso.2019.12.017.
[6] Stijns RCH, de Graaf EJR, Punt CJA, Nagtegaal ID, Nuyttens JJME, van Meerten E, et al. Long-term Oncological and Functional Outcomes of Chemoradiotherapy Followed by Organ-Sparing Transanal Endoscopic Microsurgery for Distal Rectal Cancer: the CARTS Study. JAMA Surg 2019;154:47–54. https://doi.org/10.1001/jamasurg.2018.3752.
[7] Bach SP, Gilbert A, Brock K, Korsgen S, Geh I, Hill J, et al. Radical surgery versus organ preservation via short-course radiotherapy followed by transanal endoscopic microsurgery for early-stage rectal cancer (TREC): a randomised, open-label feasibility study. Lancet Gastroenterol Hepatol 2021;6:92–105. https://doi.org/10.1016/S2468-1253(20)30333-2.
[8] Hearn N, Atwell D, Cahill K, Elks J, Vignarajah D, Lagopoulos J, et al. Neoadjuvant Radiotherapy Dose Escalation in locally Advanced Rectal Cancer: a Systematic Review and Meta-analysis of Modern Treatment Approaches and Outcomes. Clin Oncol (R Coll Radiol) 2021;33:e1–. https://doi.org/10.1016/j.clon.2020.06.008.
[9] Delishaj D, Fumagalli IC, Ursino S, Cristaudo A, Colangelo F, Stefanelli A, et al. Neoadjuvant radiotherapy dose escalation for locally advanced rectal cancers in the new era of radiotherapy: a review of literature. World J Clin Cases 2021;9:9077–89. https://doi.org/10.12998/wjcc.v9.i30.9077.
[10] Nicosia L, Bonù ML, Angelicone I, Lunardi G, Niespolo RM, Zannetti M, et al. Analysis of patients with locally advanced rectal cancer given neoadjuvant radiochemotherapy with or without RT dose intensification: a multicenter retrospective study – ATLANTIS part I. Radiother Oncol 2025;204. https://doi.org/10.1016/j.radonc.2024.110701.
[11] Taha AA, Hanbury A. Metrics for evaluating 3D medical image segmentation: analysis, selection, and tool. BMC Med Imaging 2015;15:29. https://doi.org/10.1186/s12880-015-0068-x.
[12] Appelt AL, Pløen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. Int J Radiat Oncol Biol Phys 2013;85:74–80. https://doi.org/10.1016/j.ijrobp.2012.05.017.
[13] Bertocchi E, Barugola G, Nicosia L, Mazzola R, Ricchetti F, Dell'Abate P, et al. A comparative analysis between radiation dose intensification and conventional fractionation in neoadjuvant locally advanced rectal cancer: a monocentric prospective observational study. Radiol Med 2020;125:990–8. https://doi.org/10.1007/s11547-020-01189-9.
[14] Lupattelli M, Matrone F, Gambacorta MA, Osti M, Macchia G, Palazzari E, et al. Preoperative intensity-modulated radiotherapy with a simultaneous integrated boost combined with Capecitabine in locally advanced rectal cancer: short-term results of a multicentric study. Radiat Oncol 2017;12:139. https://doi.org/10.1186/s13014-017-0870-4.
[15] Zhu J, Liu F, Gu W, Lian P, Sheng W, Xu J, et al. Concomitant boost IMRT-based neoadjuvant chemoradiotherapy for clinical stage II/III rectal adenocarcinoma: results of a phase II study. Radiat Oncol 2014;9:70. https://doi.org/10.1186/1748-717X-9-70.
[16] Arbea L, Martínez-Monge R, Díaz-González JA, Moreno M, Rodríguez J, Hernández JL, et al. Four-week neoadjuvant intensity-modulated radiation therapy with concurrent capecitabine and oxaliplatin in locally advanced rectal cancer patients: a validation phase II trial. Int J Radiat Oncol Biol Phys 2012;83:587–93. https://doi.org/10.1016/j.ijrobp.2011.06.2008.
[17] Macchia G, Gambacorta MA, Masciocchi C, Chiloiro G, Mantello G, di Benedetto M, et al. Time to surgery and pathologic complete response after neoadjuvant chemoradiation in rectal cancer: a population study on 2094 patients. Clin Transl Radiat Oncol 2017;4:8–14. https://doi.org/10.1016/j.ctro.2017.04.004.
[18] Burbach JPM, den Harder AM, Intven M, van Vulpen M, Verkooijen HM, Reerink O. Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: a systematic review and meta-analysis. Radiother Oncol 2014;113:1–9. https://doi.org/10.1016/j.radonc.2014.08.035.
[19] Socha J, Żółciak-Siwińska A, Bujko K. Radio- or Chemotherapy Dose Escalation for Organ Preservation in Rectal Cancer? J Clin Oncol 2023;41:417. https://doi.org/10.1200/JCO.22.01296.
[20] Glynne-Jones R, Hughes R. Critical appraisal of the "wait and see" approach in rectal cancer for clinical complete responders after chemoradiation. Br J Surg 2012;99:897–909. https://doi.org/10.1002/bjs.8732.
[21] Habr-Gama A, Sabbaga J, Gama-Rodrigues J, São Julião GP, Proscurshim I, Bailão Aguilar P, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum 2013;56:1109–17. https://doi.org/10.1097/DCR.0b013e3182a25c4e.
[22] López-Campos F, Martín-Martín M, Fornell-Pérez R, García-Pérez JC, Die-Trill J, Fuentes-Mateos R, et al. Watch and wait approach in rectal cancer: current controversies and future directions. World J Gastroenterol 2020;26:4218–39. https://doi.org/10.3748/wjg.v26.i29.4218.
[23] Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative complications following surgery for rectal cancer. Ann Surg 2010;251:807–18. https://doi.org/10.1097/SLA.0b013e3181dae4ed.
[24] NCCN guidelines rectal cancer. NCCN n.d. https://www.nccn.org/guidelines/guidelines-detail (accessed June 21, 2022).
[25] Nagtegaal ID, van de Velde CJH, Marijnen CAM, van Krieken JHJM, Quirke P, Dutch Colorectal Cancer Group, et al. Low rectal cancer: a call for a change of approach in abdominoperineal resection. J Clin Oncol 2005;23:9257–64. https://doi.org/10.1200/JCO.2005.02.9231.
[26] Marr R, Birbeck K, Garvican J, Macklin CP, Tiffin NJ, Parsons WJ, et al. The modern abdominoperineal excision: the next challenge after total mesorectal excision. Ann Surg 2005;242:74–82. https://doi.org/10.1097/01.sla.0000167926.60908.15.
[27] Cirocco WC. Outcomes of rectal resection following neoadjuvant therapy in the elderly: can rectal cancer patients be too old for a neoadjuvant approach? Am J Surg 2018;215:436–9. https://doi.org/10.1016/j.amjsurg.2017.10.049.
[28] Fokas E, Glynne-Jones R, Fleischmann M, Piso P, Tselis N, Ghadimi M, et al. Radiotherapy dose escalation using endorectal brachytherapy in elderly and frail patients with rectal cancer unsuitable for surgery: Lessons from studies in fit patients and future perspectives. Cancer Treat Rev 2023;112. https://doi.org/10.1016/j.ctrv.2022.102490.
[29] Hathout L, Maloney-Patel N, Malhotra U, Wang S-J, Chokhavatia S, Dalal I, et al. Management of locally advanced rectal cancer in the elderly: a critical review and algorithm. J Gastrointest Oncol 2018;9:363–76. https://doi.org/10.21037/jgo.2017.10.10.
[30] Haak HE, Maas M, Lambregts DMJ, Beets-Tan RGH, Beets GL, Melenhorst J, et al. Is watch and wait a safe and effective way to treat rectal cancer in older patients? Eur J Surg Oncol 2020;46:358–62. https://doi.org/10.1016/j.ejso.2020.01.005.
[31] Karaca S, Aysenur Arli Karacam K. A comparison of dosimetric and clinical parameters between different IMRT boost techniques in preoperative rectal cancer. J BUON 2021;26:1231–8.
[32] Adli M, Ozturk F, Degerli AD. Simultaneous Integrated Versus Sequential boost with VMAT in Neoadjuvant Radiotherapy of Rectal Cancer: a Dosimetric Study. Int J Radiat Oncol Biol Phys 2020;108. https://doi.org/10.1016/j.ijrobp.2020.07.1949.
[33] Van den Begin R, Kleijnen J-P, Engels B, Philippens M, van Asselen B, Raaymakers B, et al. Tumor volume regression during preoperative chemoradiotherapy for rectal cancer: a prospective observational study with weekly MRI. Acta Oncol 2018;57:723–7. https://doi.org/10.1080/0284186X.2017.1400689.
[34] Devic S, Bekerat H, Garant A, Vuong T. Optimization of HDRBT boost dose delivery for patients with rectal cancer. Brachytherapy 2019;18:559–63. https://doi.org/10.1016/j.brachy.2019.02.001.
[35] Garant A, Vasilevsky C-A, Boutros M, Khosrow-Khavar F, Kavan P, Diec H, et al. MORPHEUS phase II–III Study: a Pre-Planned Interim Safety Analysis and Preliminary results. Cancers (Basel) 2022;14:3665. https://doi.org/10.3390/cancers14153665.
[36] Jensen LH, Risum S, Nielsen JD, Mynster T, Ploeen J, Rahr HB, et al. Curative chemoradiation for low rectal cancer: Primary clinical outcomes from a multicenter phase II trial. JCO 2022;40. https://doi.org/10.1200/JCO.2022.40.17_suppl.LBA3514.
[37] Vejle Hospital. Randomized Trial of Standard Dose Versus High Dose of Radiotherapy in Rectal Preservation With Chemo-radiotherapy to Patients With Early Low and Mid Rectal Cancer: The Watchful Waiting 3 Trial (WW3). clinicaltrials.gov; 2023.
[38] Chiloiro G, Romano A, Cusumano D, Boldrini L, Panza G, Placidi L, et al. THeragnostic utilities for neoplastic DisEases of the rectum by MRI guided radiotherapy (THUNDER 2) phase II trial: interim safety analysis. Radiat Oncol 2023;18:163. https://doi.org/10.1186/s13014-023-02353-x.
[39] Chiloiro G, Cusumano D, Boldrini L, Romano A, Placidi L, Nardini M, et al. THUNDER 2: THeragnostic Utilities for Neoplastic DisEases of the Rectum by MRI guided radiotherapy. BMC Cancer 2022;22:67. https://doi.org/10.1186/s12885-021-09158-9.
[40] Gani C, Lo Russo M, Boeke S, Wegener D, Gatidis S, Butzer S, et al. A novel approach for radiotherapy dose escalation in rectal cancer using online MR-guidance and rectal ultrasound gel filling - Rationale and first in human. Radiother Oncol 2021;164:37–42. https://doi.org/10.1016/j.radonc.2021.09.002.
[41] Chiloiro G, Gani C, Boldrini L. Rectal Cancer MRI Guided Radiotherapy: a Practical Review for the physician. Semin Radiat Oncol 2024;34:64–8. https://doi.org/10.1016/j.semradonc.2023.10.004.
[42] Colaco RJ, Nichols RC, Huh S, Getman N, Ho MW, Li Z, et al. Protons offer reduced bone marrow, small bowel, and urinary bladder exposure for patients receiving neoadjuvant radiotherapy for resectable rectal cancer. J Gastrointest Oncol 2014;5:3–8. https://doi.org/10.3978/j.issn.2078-6891.2013.041.
[43] Fok M, Toh S, Easow J, Fowler H, Clifford R, Parsons J, et al. Proton beam therapy in rectal cancer: a systematic review and meta-analysis. Surg Oncol 2021;38. https://doi.org/10.1016/j.suronc.2021.101638.
[44] Kumar T, Schernberg A, Busato F, Laurans M, Fumagalli I, Dumas I, et al. Correlation between pelvic bone marrow radiation dose and acute hematological toxicity in cervical cancer patients treated with concurrent chemoradiation. Cancer Manag Res 2019;11:6285–97. https://doi.org/10.2147/CMAR.S195989.
[45] Havenga K, Maas CP, DeRuiter MC, Welvaart K, Trimbos JB. Avoiding long-term disturbance to bladder and sexual function in pelvic surgery, particularly with

rectal cancer. Semin Surg Oncol 2000;18:235–43. https://doi.org/10.1002/(sici)1098-2388(200004/05)18:3<235::aid-ssu7>3.0.co;2-7.
[46] NHS commissioning » Proton beam therapy n.d. https://www.england.nhs.uk/commissioning/spec-services/highly-spec-services/pbt/ (accessed March 17, 2024).
[47] Verma V, Mishra MV, Mehta MP. A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. Cancer 2016;122:1483–501. https://doi.org/10.1002/cncr.29882.
[48] Meldolesi E, Chiloiro G, Giannini R, Menghi R, Persiani R, Corvari B, et al. The Role of Simultaneous Integrated boost in locally Advanced Rectal Cancer patients with positive Lateral Pelvic Lymph Nodes. Cancers (Basel) 2022;14:1643. https://doi.org/10.3390/cancers14071643.
[49] Couwenberg AM, Burbach JPM, Berbee M, Lacle MM, Arensman R, Raicu MG, et al. Efficacy of Dose-Escalated Chemoradiation on complete Tumor Response in patients with locally Advanced Rectal Cancer (RECTAL-BOOST): a phase 2 Randomized Controlled Trial. Int J Radiat Oncol Biol Phys 2020;108:1008–18. https://doi.org/10.1016/j.ijrobp.2020.06.013.
[50] Alongi F, Fersino S, Mazzola R, Fiorentino A, Giaj-Levra N, Ricchetti F, et al. Radiation dose intensification in pre-operative chemo-radiotherapy for locally advanced rectal cancer. Clin Transl Oncol 2017;19:189–96. https://doi.org/10.1007/s12094-016-1522-0.
[51] Engels B, Tournel K, Everaert H, Hoorens A, Sermeus A, Christian N, et al. Phase II study of preoperative helical tomotherapy with a simultaneous integrated boost for rectal cancer. Int J Radiat Oncol Biol Phys 2012;83:142–8. https://doi.org/10.1016/j.ijrobp.2011.05.068.
[52] Peters FP, Teo MTW, Appelt AL, Bach S, Baatrup G, de Wilt JHW, et al. Mesorectal radiotherapy for early stage rectal cancer: a novel target volume. Clinical and Translational Radiation Oncology 2020;21:104–11. https://doi.org/10.1016/j.ctro.2020.02.001.
[53] Valentini V, Gambacorta MA, Cellini F, Aristei C, Coco C, Barbaro B, et al. The INTERACT Trial: long-term results of a randomised trial on preoperative capecitabine-based radiochemotherapy intensified by concomitant boost or oxaliplatin, for cT2 (distal)-cT3 rectal cancer. Radiother Oncol 2019;134:110–8. https://doi.org/10.1016/j.radonc.2018.11.023.
[54] Prata I, Eriksson M, Krdzalic J, Kranenbarg EM-K, Roodvoets AGH, Beets-Tan R, et al. Results of a diagnostic imaging audit in a randomised clinical trial in rectal cancer highlight the importance of careful planning and quality control. Insights. Imaging 2023;14:206. https://doi.org/10.1186/s13244-023-01552-0.
[55] Beets-Tan RGH, Lambregts DMJ, Maas M, Bipat S, Barbaro B, Curvo-Semedo L, et al. Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol 2018;28:1465–75. https://doi.org/10.1007/s00330-017-5026-2.
[56] Sluckin TC, Couwenberg AM, Lambregts DMJ, Hazen S-MJA, Horsthuis K, Meijnen P, et al. Lateral Lymph Nodes in Rectal Cancer: do we all think the same? a Review of Multidisciplinary Obstacles and Treatment Recommendations. Clin Colorectal Cancer 2022;21:80–8. https://doi.org/10.1016/j.clcc.2022.02.002.
[57] Lee S, Kassam Z, Baheti AD, Hope TA, Chang KJ, Korngold EK, et al. Rectal cancer lexicon 2023 revised and updated consensus statement from the Society of Abdominal Radiology Colorectal and Anal Cancer Disease-Focused Panel. Abdom Radiol (NY) 2023;48:2792–806. https://doi.org/10.1007/s00261-023-03893-2.
[58] Gollub MJ, Arya S, Beets-Tan RG, dePrisco G, Gonen M, Jhaveri K, et al. Use of magnetic resonance imaging in rectal cancer patients: Society of Abdominal Radiology (SAR) rectal cancer disease-focused panel (DFP) recommendations 2017. Abdom Radiol (NY) 2018;43:2893–902. https://doi.org/10.1007/s00261-018-1642-9.
[59] Ganem J, Thureau S, Gardin I, Modzelewski R, Hapdey S, Vera P. Delineation of lung cancer with FDG PET/CT during radiation therapy. Radiat Oncol 2018;13:219. https://doi.org/10.1186/s13014-018-1163-2.
[60] Berthelsen AK, Dobbs J, Kjellén E, Landberg T, Möller TR, Nilsson P, et al. What's new in target volume definition for radiologists in ICRU Report 71? how can the ICRU volume definitions be integrated in clinical practice? Cancer Imaging 2007;7:104–16. https://doi.org/10.1102/1470-7330.2007.0013.
[61] Borgheresi A, De Muzio F, Agostini A, Ottaviani L, Bruno A, Granata V, et al. Lymph Nodes Evaluation in Rectal Cancer: where do we stand and Future Perspective. J Clin Med 2022;11:2599. https://doi.org/10.3390/jcm11092599.
[62] Ballonoff A, Kavanagh B, McCarter M, Kane M, Pearlman N, Nash R, et al. Preoperative capecitabine and accelerated intensity-modulated radiotherapy in locally advanced rectal cancer: a phase II trial. Am J Clin Oncol 2008;31:264–70. https://doi.org/10.1097/COC.0b013e318161dbd3.
[63] Kim YC, Lim JS, Keum KC, Kim KA, Myoung S, Shin SJ, et al. Comparison of diffusion-weighted MRI and MR volumetry in the evaluation of early treatment outcomes after preoperative chemoradiotherapy for locally advanced rectal cancer. J Magn Reson Imaging 2011;34:570–6. https://doi.org/10.1002/jmri.22696.
[64] Lambrecht M, Vandecaveye V, De Keyzer F, Roels S, Penninckx F, Van Cutsem E, et al. Value of diffusion-weighted magnetic resonance imaging for prediction and early assessment of response to neoadjuvant radiochemotherapy in rectal cancer: preliminary results. Int J Radiat Oncol Biol Phys 2012;82:863–70. https://doi.org/10.1016/j.ijrobp.2010.12.063.
[65] Palmisano A, Esposito A, Di Chiara A, Ambrosi A, Passoni P, Slim N, et al. Could early tumour volume changes assessed on morphological MRI predict the response to chemoradiation therapy in locally-advanced rectal cancer? Clin Radiol 2018;73:555–63. https://doi.org/10.1016/j.crad.2018.01.007.
[66] Fiorino C, Gumina C, Passoni P, Palmisano A, Broggi S, Cattaneo GM, et al. A TCP-based early regression index predicts the pathological response in neo-adjuvant radio-chemotherapy of rectal cancer. Radiother Oncol 2018;128:564–8. https://doi.org/10.1016/j.radonc.2018.06.019.
[67] Hofheinz R-D, Fokas E, Benhaim L, Price TJ, Arnold D, Beets-Tan R, et al. Localised rectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2025;36:1007–24. https://doi.org/10.1016/j.annonc.2025.05.528.
[68] Tey J, Leong CN, Cheong WK, Sze TG, Yong WP, Tham IWK, et al. A phase II trial of preoperative concurrent chemotherapy and dose escalated intensity modulated radiotherapy (IMRT) for locally advanced rectal cancer. J Cancer 2017;8:3114–21. https://doi.org/10.7150/jca.21237.
[69] Sun Myint A, Rao C, Barbet N, Thamphya B, Pace-Loscos T, Schiappa R, et al. The safety and efficacy of total mesorectal excision (TME) surgery following dose-escalation: Surgical outcomes from the organ preservation in early rectal adenocarcinoma (OPERA) trial, a European multicentre phase 3 randomised trial (NCT02505750). Colorectal Dis 2023;25:2160–9. https://doi.org/10.1111/codi.16773.
[70] Vendrely V, Rivin Del Campo E, Modesto A, Jolnerowski M, Meillan N, Chiavassa S, et al. Rectal cancer radiotherapy. Cancer Radiother 2022;26:272–8. https://doi.org/10.1016/j.canrad.2021.11.002.
[71] Mayo CS, Moran JM, Bosch W, Xiao Y, McNutt T, Popple R, et al. American Association of Physicists in Medicine Task Group 263: Standardizing Nomenclatures in Radiation Oncology. Int J Radiat Oncol Biol Phys 2018;100:1057–66. https://doi.org/10.1016/j.ijrobp.2017.12.013.

Giuditta Chiloiro[a], Angela Romano[a,b,*], Regina Beets-Tan[c,d,e], Krzysztof Bujko[f], Davide Cusumano[g], Emmanouil Fokas[h], Karin Haustermans[i], Florence Huguet[j], Martijn PW Intven[k], Corrie AM Marijnen[l,m], Ilaria Nacci[a], Iris D Nagtegaal[n], Femke P Peters[m], Alexandra Stewart[o], Vincenzo Valentini[p], Maria Antonietta Gambacorta[a,b]

[a] *Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy*
[b] *Università Cattolica del Sacro Cuore, Rome, Italy*
[c] *Department of Diagnostic Oncology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands*
[d] *GROW School for Oncology and Reproduction, Maastricht University, Maastricht, the Netherlands*
[e] *Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark*
[f] *Department of Radiotherapy I, M. Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[g] *Mater Olbia Hospital, Olbia, Sassari, Italy*
[h] *Department of Radiation Oncology, Cyberknife and Radiotherapy, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD), Faculty of Medicine Cologne, University Hospital Cologne, Cologne, Germany*
[i] *Department of Radiation Oncology, University Hospitals Leuven 3000 Leuven, Belgium*
[j] *Service d'oncologie radiothérapie, hôpital Tenon, AP-HP, Sorbonne université, Paris, France*
[k] *Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, the Netherlands*
[l] *Department of Radiation Oncology, Leiden University Medical Centre, Leiden, the Netherlands*
[m] *Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands*
[n] *Department of Pathology, Radboud University Medical Centre, Nijmegen, the Netherlands*
[o] *Royal Surrey Hospital, NHS Foundation trust, Guildford, United Kingdom*
[p] *Centro Eccellenza Oncologia e Diagnostica per Immagini, Ospedale Isola Tiberina - Gemelli Isola, Rome, Italy*

[*] Corresponding author at: Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy.
E-mail address: angela.romano@policlinicogemelli.it (A. Romano).