

# Clinical Target Volume Definition in Preoperative Radiotherapy of Rectal Carcinoma: a Systematic Review

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## Abstract

**Purpose of Review** Preoperative radiotherapy (RT) or chemoradiation represents a standard option in neoadjuvant treatment of rectal cancer (RC). The aim of this analysis is to present a systematic review of clinical target volume (CTV) definition in preoperative RT of RC.

A systematic review of published literature was performed. Studies providing clear indications for CTV definition in preoperative RT of RC were eligible. Only studies published as full text were considered. The search was restricted to English, German, and French languages. The CTV delineation, based

on the different guidelines, was drawn on selected slices of a CT scan and the CTV definition based on different guidelines was reported in a table to facilitate the comparison.

**Recent Findings** A total of six publications containing indications for CTV delineation fulfilled the selection criteria and were included in our review. The studies showed a large variability in available indications between CTV contouring guidelines of RC, partly arising from differences in methods used to propose the single guidelines: expert opinion, systematic review, computer-generated consensus, and 3D modeling of recurrence sites.

**Summary** In our systematic analysis, the available indications for CTV definition in preoperative RT of RC were reviewed. A large variation in target volume delineation was observed.

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**Keywords** Radiotherapy · Rectal cancer · Contouring · Target · Review

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## Introduction

Colorectal cancer ranks among the top five causes of cancer death in developed countries with an increasing incidence over the last decade, especially in the older population. Rectal cancer (RC), in particular, is the cause of more than a quarter of these deaths [1].

Radiotherapy (RT), with or without the use of concomitant chemotherapy, represents a standard option in neoadjuvant treatment of locally advanced RC. To improve the sphincter preservation rate and reduce the locoregional failure rate, pelvic RT is routinely used in patients with stage II–III disease [2, 3]. Several randomized controlled trials showed that

preoperative RT or chemoradiotherapy (CRT) is able to improve local control and overall survival [4–6]. With the diffusion of the conformal techniques and in particular of intensity-modulated radiation therapy (IMRT), the problem of clinical target volume (CTV) definition is particularly critical.

Recently, several studies showed marked interobserver variability in the CTV definition of RC [7, 8] suggesting that such variability could be significantly reduced by the use of guidelines and atlases [7–9]. In the past, a number of indications and guidelines on this subject have been proposed [7, 10–14] and recently an international guidelines consensus has been proposed [15]. Based on the high incidence of RC and on the relevance of a correct CTV definition, the aim of the current study is to systematically review the available guidelines on CTV definition in preoperative RT of rectal cancer.

## Materials and Methods

### Study Sources and Searches

We developed a protocol for the review and followed standard reporting guidelines [16]. We performed a comprehensive literature search by using PubMed, SCOPUS, Google Scholar, and the Cochrane Central Register of Clinical Trials to identify full articles evaluating the definition of CTV in preoperative RT of rectal cancer. [ClinicalTrials.gov](http://ClinicalTrials.gov) was searched for ongoing or recently completed trials, and the International Prospective Register of Systematic Reviews (PROSPERO, [www.crd.york.ac.uk/prospéro/](http://www.crd.york.ac.uk/prospéro/)) was searched for ongoing or recently completed systematic reviews. Electronic searches were supplemented by manual searches of references of included studies and review articles. We identified studies using the following medical subject headings (MeSH) and keywords including the following: “rectum,” “radiotherapy,” “contouring,” “target,” “clinical target volume,” “CTV,” “preoperative.” The Medline search strategy was as follows: (“rectal neoplasms” [MeSH Terms] OR (“rectal” [All Fields] AND “neoplasms” [All Fields]) OR “rectal neoplasms” [All Fields] OR (“rectal” [All Fields] AND “cancer” [All Fields]) OR “rectal cancer” [All Fields]) AND (“radiotherapy” [Subheading] OR “radiotherapy” [All Fields] OR “radiotherapy” [MeSH Terms])) AND (contouring [All Fields] OR target [All Fields]). The search was restricted to English, German, and French languages.

### Selection Process

Two review authors (AB, MG) independently screened the titles and abstracts yielded by the search against the inclusion criteria. Full reports were obtained for all titles that appeared to meet the inclusion criteria or where there was any uncertainty. Review authors screened the full text reports and

decided whether these met the inclusion criteria. Disagreements were resolved through discussion of all the authors.

### Data Extraction

Using standardized forms, two reviewers (AB, MG) extracted data independently and in duplicate from each eligible study. Reviewers resolved disagreements by discussion, and one arbitrator (AGM) adjudicated unresolved disagreements. From each study were extracted data about inclusion in the CTV of several volumes (presacral space, mesorectum, internal iliac nodes, external iliac nodes, sphincter complex, obturator lymph nodes, ischioanal fossa, and inguinal lymph nodes) depending on tumor characteristics (cTstage, cNstage, tumor site).

### Inclusion and Exclusion Criteria

To be included in the systematic review, we required studies that provided clear indications for CTV definition in the preoperative RT of RC. Only studies published as full text were considered. Commentaries, letters, and editorials were not excluded during screening but were considered only if reporting original data. Exclusion criteria included studies providing only indications about gross tumor volume (GTV) or planning target volume (PTV) and studies published only in abstract form. Finally, a consensus agreement among experts was reached by means of a videoconference meeting as previously described [17].

### Analysis of the Studies

One male patient with locally advanced (cT3 cN1 M0) rectal cancer (middle-high rectum) was selected. The CTV delineation, based on the different guidelines, was drawn on selected slices of a CT scan performed on this patient. Furthermore, the methods of defining the CTV based on different guidelines were reported in a table in order to facilitate the comparison.

### Integration of the Published Guidelines

We tested the possibility to integrate the different recommendations. The criteria used were mainly the following: (1) incorporate all indications without changes if uniform consensus is available, (2) incorporate as far as possible any proposal of “modulation” based on disease characteristics, and (3) use contouring criteria as possibly “practical” and based on the use of a CT without i.v. contrast medium.

## Results

Through bibliographic research and paper selection, performed as described in Fig. 1, six publications containing indications for CTV delineation were selected.

### Studies Description

Lorchel and colleagues published guidelines for rectal tumor contouring. Based on the dramatic reduction in local recurrence rate after the introduction of total mesorectal excision (TME), the authors identified the mesorectum as the only site to be included in the CTV in all patients. Various methods of CTV extension based on the characteristics of local invasion of the disease were also proposed. CTV of nodal areas was not considered [11].

Roels and coworkers carried out a systematic literature review on most common sites of local/nodal recurrence in patients with rectal cancer who underwent surgery. Based on collected data, anatomic subsites based on different risk of involvement were identified. In addition, according to tumor site and stage, detailed indications for CTV definition were proposed, including mesorectum and posterior pelvic site in all patients and lateral nodal space in most of these [14].

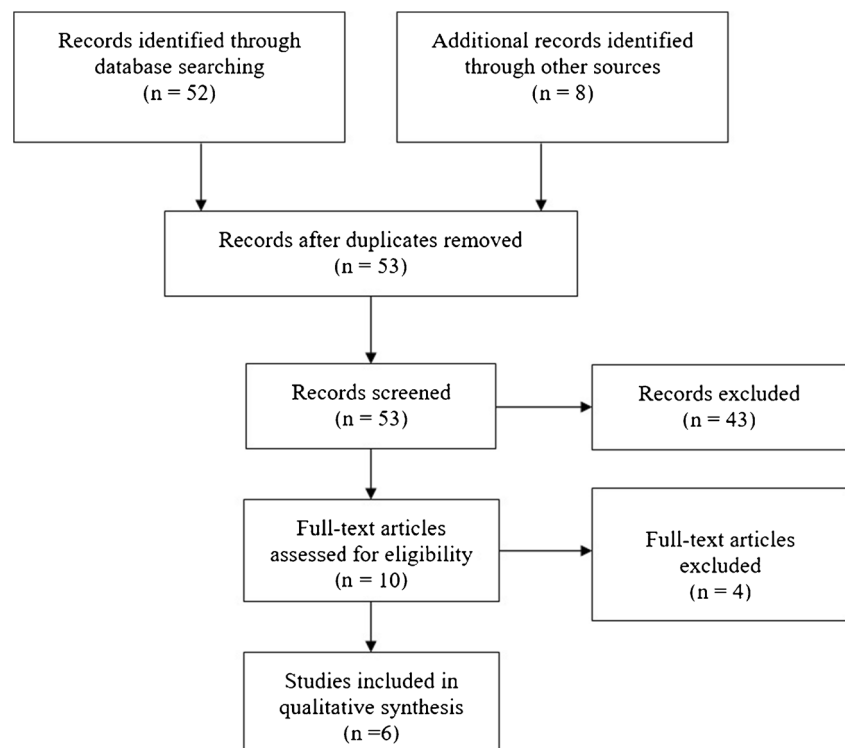
Myerson and colleagues, in order to standardize the anorectal cancer contouring in RTOG trials, reported the recommendations of a consensus panel of experts who developed a practical atlas for conformal treatment of these tumors. Nine

different radiation oncologists proposed their contouring, dividing it into three different “elective” CTVs. Using an application to calculate the index of confidence, a *computer-generated consensus contour* was estimated and subsequently optimized through discussion between the different authors to achieve the final version [12].

Nijkamp and coworkers analyzed the pelvic recurrence sites in patients enrolled in the Dutch total mesorectal excision trial. Using a three-dimensional model, they assessed 94 patients with recurrence after surgery alone (69 patients) or after surgery preceded by radiotherapy (25 patients). The results of this analysis showed that of the patients without lymph node involvement and with negative circumferential and radial margin (CRM), in only one patient, the site of relapse was above the S2–S3 interspaces. Therefore, the authors concluded that in patients without nodal and CRM involvement, undergoing preoperative RT followed by TME, the CTV cranial margin can be lowered to the S2–S3 levels [13].

Gambacorta and colleagues evaluated the efficacy of an *atlas-based auto-segmentation system* for locally advanced RC contouring. The authors reported the utility of this system mainly in the educational/training setting. The criteria used for inclusion in the CTV of the different anatomic subsites were presented. In particular, the authors proposed a modulation of nodal irradiation based on macroscopic lymph node involvement. For reasons of contiguity, for example, obturator lymph

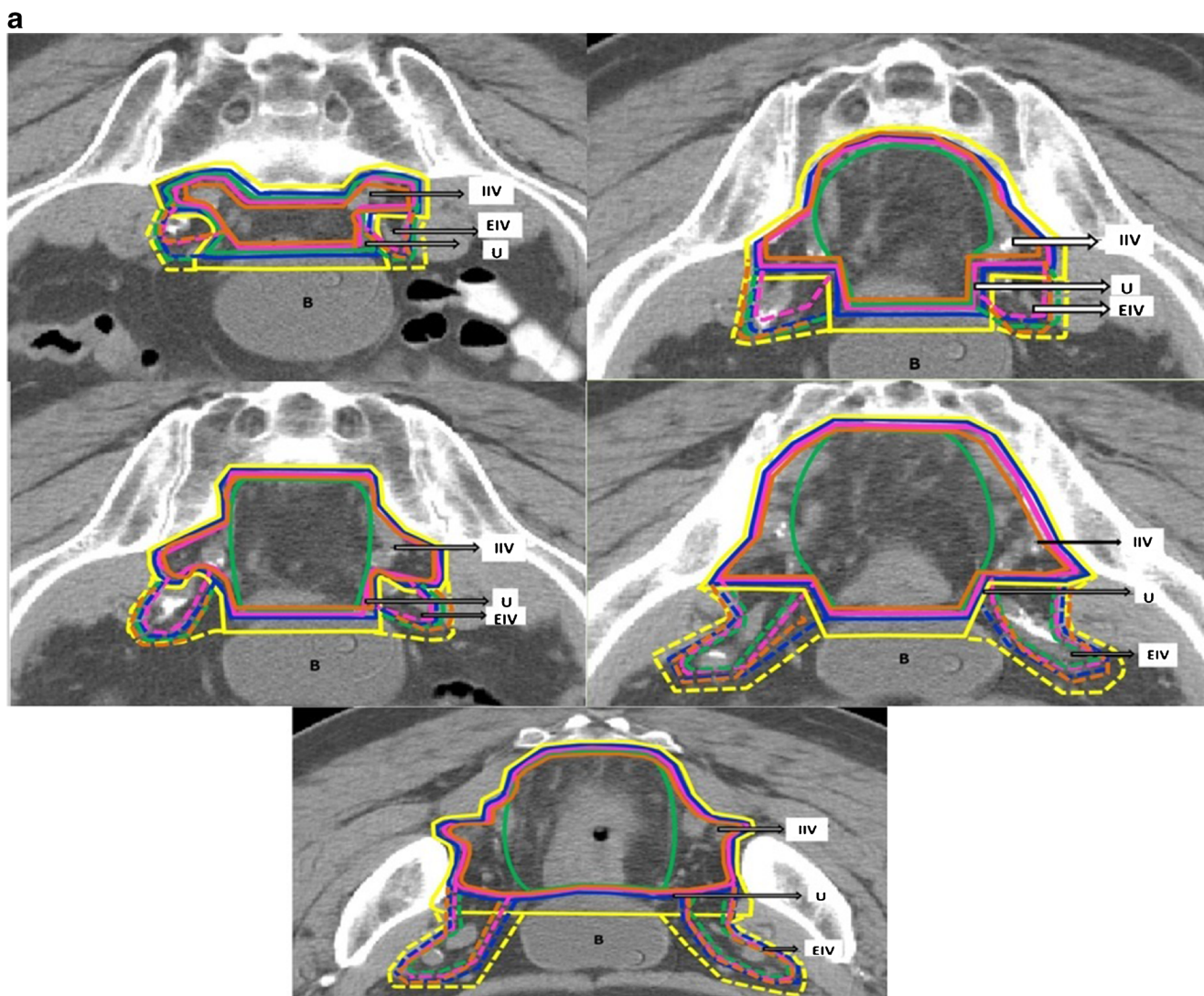
**Fig. 1** Process of selection of papers



**Table 1** Definition of CTV in the different guidelines

Author/year	Presacral space	Mesorectum	Internal iliac lymph nodes	External iliac lymph nodes	Sphincter complex	Obturator lymph nodes	Ischiorectal fossa	Inguinal lymph nodes
Lorchel [11]	No except if the tumor invades the superior pelvic-rectal space	Yes for cancers of the middle and lower rectum where the margin is less than 2 cm from the anal sphincter	No except if these nodes are a drain station of organs invaded by the tumor	No except if these nodes are a drain station of organs invaded by the tumor	Yes if: -tumor located <2 cm from the anal sphincter -required abdominoperineal amputation	No except if these nodes are a drain station of organs invaded by the tumor	Yes if: -tumor located <2 cm from the anal sphincter -required abdominoperineal	No except if these nodes are a drain station of organs invaded by the tumor
Roels [14]	Yes	Yes	Yes	No except if the anterior organ involvement is highly suspect	No except if: -surgical aim is to save the sphincter and the tumor is located <6 cm from the anal verge; -tumor invades the sphincter (required abdominoperineal resection)	No except if the tumor is located <10 cm from the anal verge	No except if: -surgical aim is to save the sphincter and the tumor is located <6 cm from the anal verge; -tumor invades the sphincter (required abdominoperineal resection);	Yes if: - lower third of the vagina involvement -internal and external anal sphincter involvement
Myerson [12]	Yes	Yes	Yes	No except in gynecological and genitourinary structures involvement; optional in case of anal canal invasion	Only the part necessary to ensure a 2 cm margin from the caudal tumor pole	Only the posterior portion of the internal obturator vessel	No except in case of direct extension	Optional in case of extension to anal canal, perianal skin or lower third of the vagina
Nijkamp [13]	Yes in patients with CRM- and N+, the cranial edge can be lowered to the S2-S3 interspace	Yes	Yes	Not described	Not described	Not described	Not described	Not described
Gambacorta [10]	Yes	Yes	Yes	No except if: -obturator lymph node involvement -Anterior pelvic organs invasion (cT4)	No except if: -abdominal-perineal resection required -low cT3	Yes except if "high" cT3	No except if: - direct tumor infiltration -low cT3	Not described
Valentini [15•]	Yes Include even abdominal presacral lymph nodes in case of positive lymph nodes in this site	Yes	Yes: in cT3N0, MRF-, the cranial limit may be lowered at the level of the bifurcation of the inferior mesenteric artery in sigmoid artery and superior rectal artery	No except if: - anterior pelvic organ infiltration and/or anal sphincter invasion - cT3 with extra mesorectal nodes	No except for anal sphincter invasion	No except if -positive nodes in the posterior lateral lymph nodes (internal iliac); -cT4; -cN2.	No except if: -direct tumor infiltration of ischiorectal fossa or external anal sphincter	No except if: -infiltration of inferior third of vagina -anal sphincter invasion





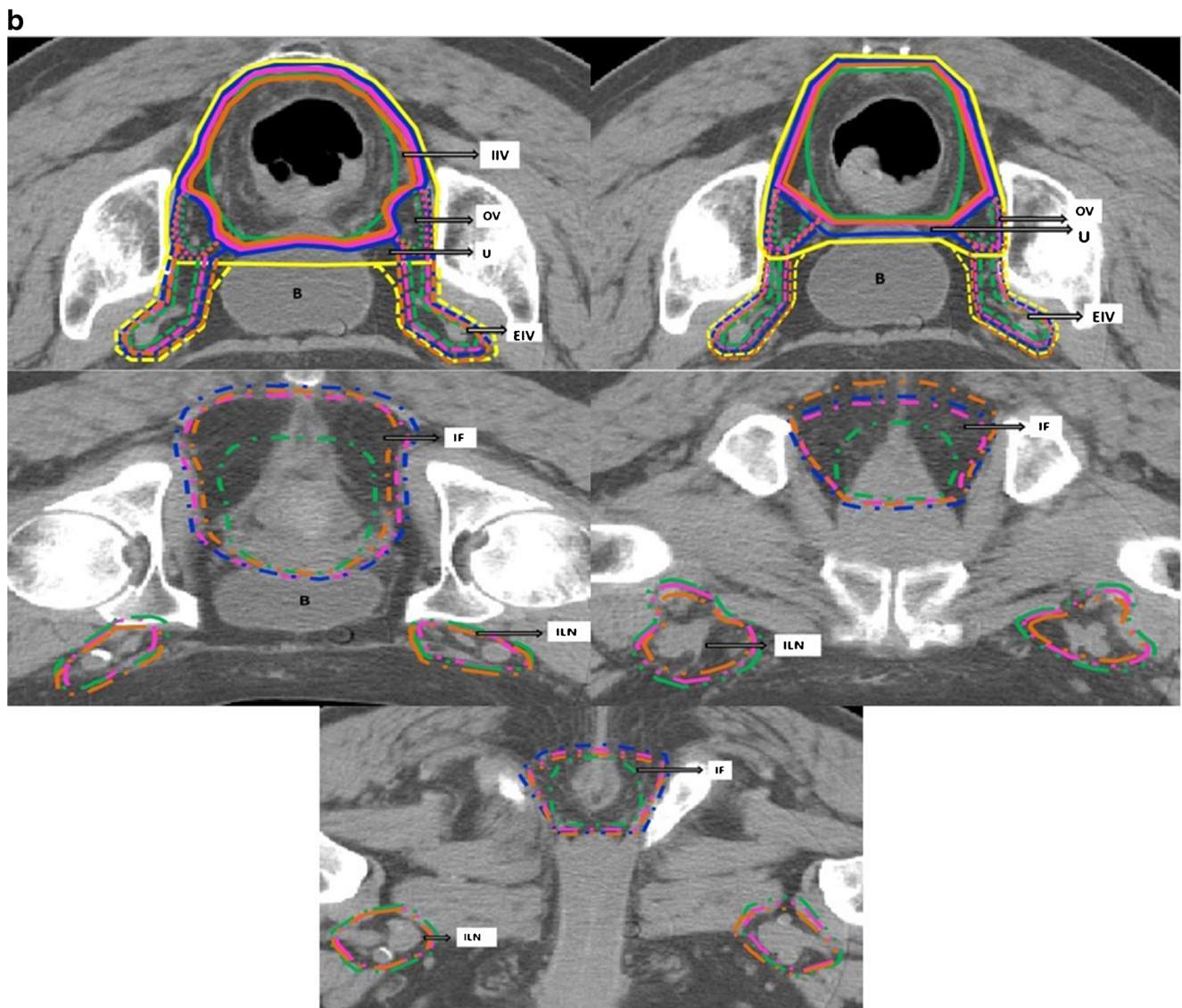
**Fig. 2 a, b** Axial CT scans illustrating differences between Lorchel et al. (green), Roels et al. (pink), Gambacorta et al. (blues) and Myerson et al. (yellow) CTV contouring guidelines, Valentini et al. (orange). External iliac lymph nodes: green dashed line = based on the organ at risk invaded; pink dashed line = anterior organ involvement; blue dashed line = involvement of the obturator lymph node or anterior organ involvement; yellow dashed line = extension into genitourinary structures or anal canal involvement; orange dashed line = anterior organ involvement, anal sphincter invasion, cT3 with extra mesorectal node. Obturator lymph nodes: green dotted line = based on the organ at risk invaded; pink dotted line = tumor <10 cm from anal margin; orange dotted line = cT3N2, anterior organ involvement, anal sphincter invasion, cT3 with extra mesorectal node. Ischio-rectal fossa: green dash-dot

line = tumor <2 cm from internal sphincter or abdominal resection required; pink dash-dot line = invasion of anal sphincter and abdominal resection required or surgery aimed to sphincter-saving resection or tumor <6 cm from anal margin; blue dash-dot line = direct tumor infiltration or low cT3; orange dash-dot line = direct tumor infiltration of ischio-rectal fossa or external anal sphincter. Inguinal lymph nodes: green dash-dot-dot line = based on the organ at risk invaded; pink dash-dot-dot line = involvement of the lower third of the vagina or extension in the internal and external anal sphincter; orange dash-dot-dot line = infiltration of inferior third vagina, anal sphincter invasion. B bladder, U ureters, IIV internal iliac vessels, EIV external iliac vessels, OV obturator vessels, IF ischio-rectal fossa, ILN inguinal lymph nodes

nodes were included in case of internal iliac node macroscopic involvement and external iliac nodes in case of obturator node macroscopic involvement [10].

Valentini and his working group of seven expert radiation oncologists across the globe compared the available published guidelines about CTV delineation on RC. They selected different clinical stages and drawn on CT scan slices CTV1 using Falcon platform following

previously published guidelines. All the radiation oncologists were authors of at least one of the published guidelines. During a meeting with several specialists on RC, a CTV proposal based on new anatomical boundaries was delineated and then the final consensus guidelines were validated. The major modifications were about lateral lymph nodes (ex-internal iliac nodes) and the ischio-rectal fossa delineation [15•].



**Fig. 2** continued.

### Analysis of the Studies

Table 1 shows and compares CTV definitions proposed by different authors in different clinical situations. Figure 2a, b shows CTV contouring according to different authors and modulated based on RC site and stage.

### Integration of Guidelines

Following the indications of all the literature guidelines [7, 10–15•], CTV included the presacral space and mesorectum in all patient categories.

In all patients, internal iliac lymph nodes were included in the CTV, as indicated by all publications except that of Lorchel and coworkers [11].

In patients with positive lymph nodes above the presacral space, abdominal presacral lymph nodes were included in the CTV [15•].

Inguinal lymph nodes were included only in case of anal sphincter or lower third of the vagina involvement, as indicated by Roels and Valentini [14, 15•]. In this case, also external iliac and obturator nodes were included.

Obturator nodes were also included in case of RC located less than 10 cm from anal verge [14], in case of macroscopic involvement of internal iliac nodes [10], and in case of cT4 tumors and/or with multiple positive lymph nodes in the mesorectum [15•].

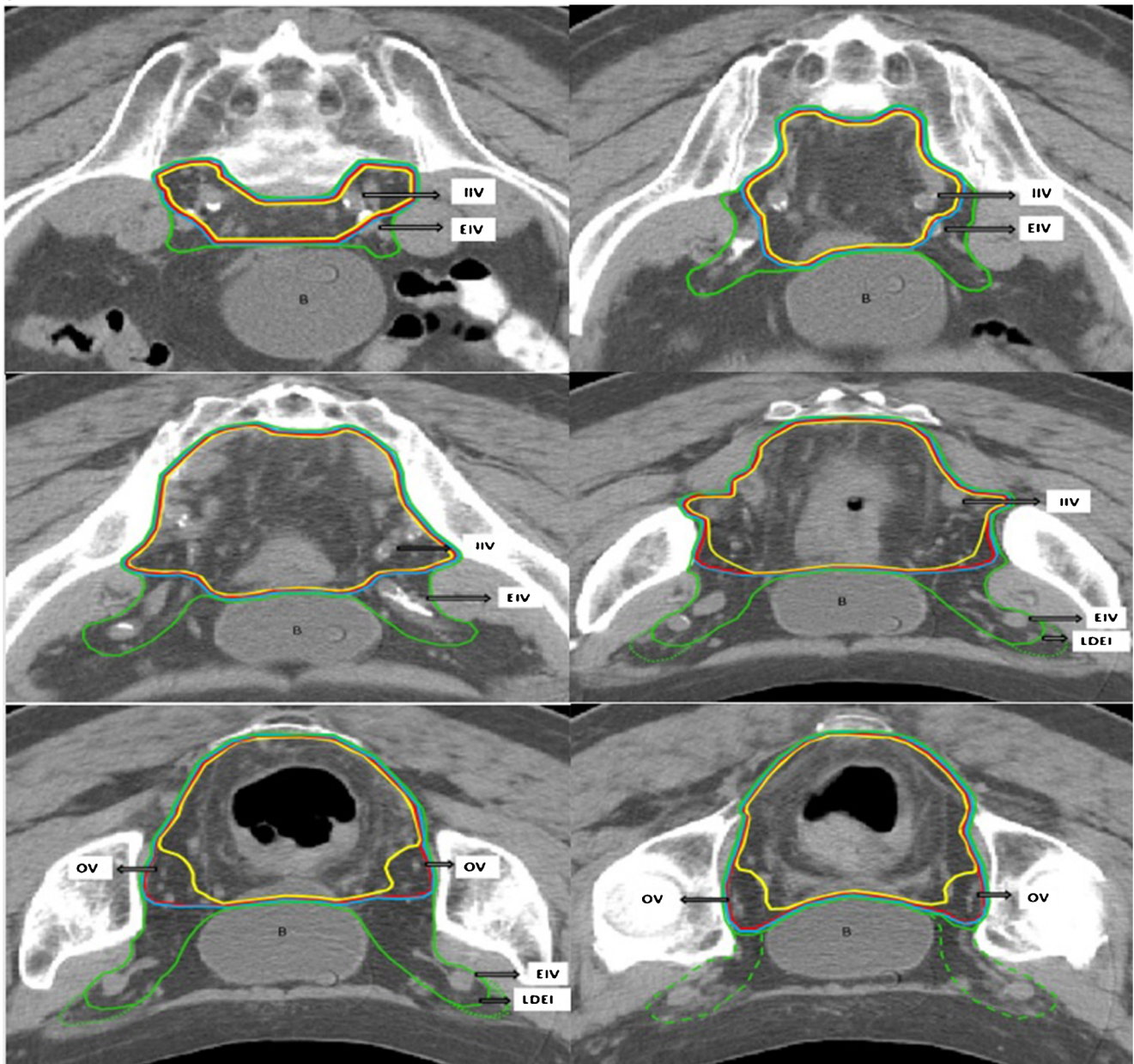
External iliac nodes were included in the target in case of tumor infiltration of the organs in the anterior pelvis [10–12, 14, 15•], in case of tumor infiltration of anal sphincter [15•], and in case of macroscopic involvement of obturator nodes [10, 15•].

**Table 2** Criteria for inclusion of the different subsites of the CTV defined by integrating the different guidelines

Clinical characteristics											
Subsites	cT3 and/or N <sub>1-</sub> <sub>2</sub> > 10 cm above the anal canal	cT3 and/or N <sub>1-</sub> <sub>2</sub> < 10 cm above the anal canal	N+ internal iliac	N+ obturator	N+ external iliac	Extensive involvement of anal sphincter and / or involvement of lower third of the vagina	Ischiorectal fossa invasion	Abdominal-perineal resection planned	cT4 (sacrum)	cT4 (anterior pelvic organs)	Presacral abdominal N+ (cranial limit: bifurcation of the aorta in common iliac arteries or 5 mm above the most cranial positive lymph node)
Presacral space and mesorectum	+	+	+	+	+	+	+	+	+	+	+
Sphincter complex	-	-	-	-	-	+	+	+	-	-	-
Ischiorectal fossa	-	-	-	-	-	+	+	-	-	-	-
Sacral canal	-	-	-	-	-	-	-	-	+	-	-
Internal iliac lymph nodes	+	+	+	+	+	+	+	+	+	+	+
Obturator lymph nodes	-	+	+	+	+	+	+	-	-	+	-
External iliac nodes (excluding lateral-distal)	-	-	-	+	+	+	-	-	-	+	-
Lateral-distal external iliac lymph nodes	-	-	-	-	+	+	-	-	-	-	-
Inguinal lymph nodes	-	-	-	-	-	+	-	-	-	-	-
Abdominal presacral space	-	-	-	-	-	-	-	-	-	-	+



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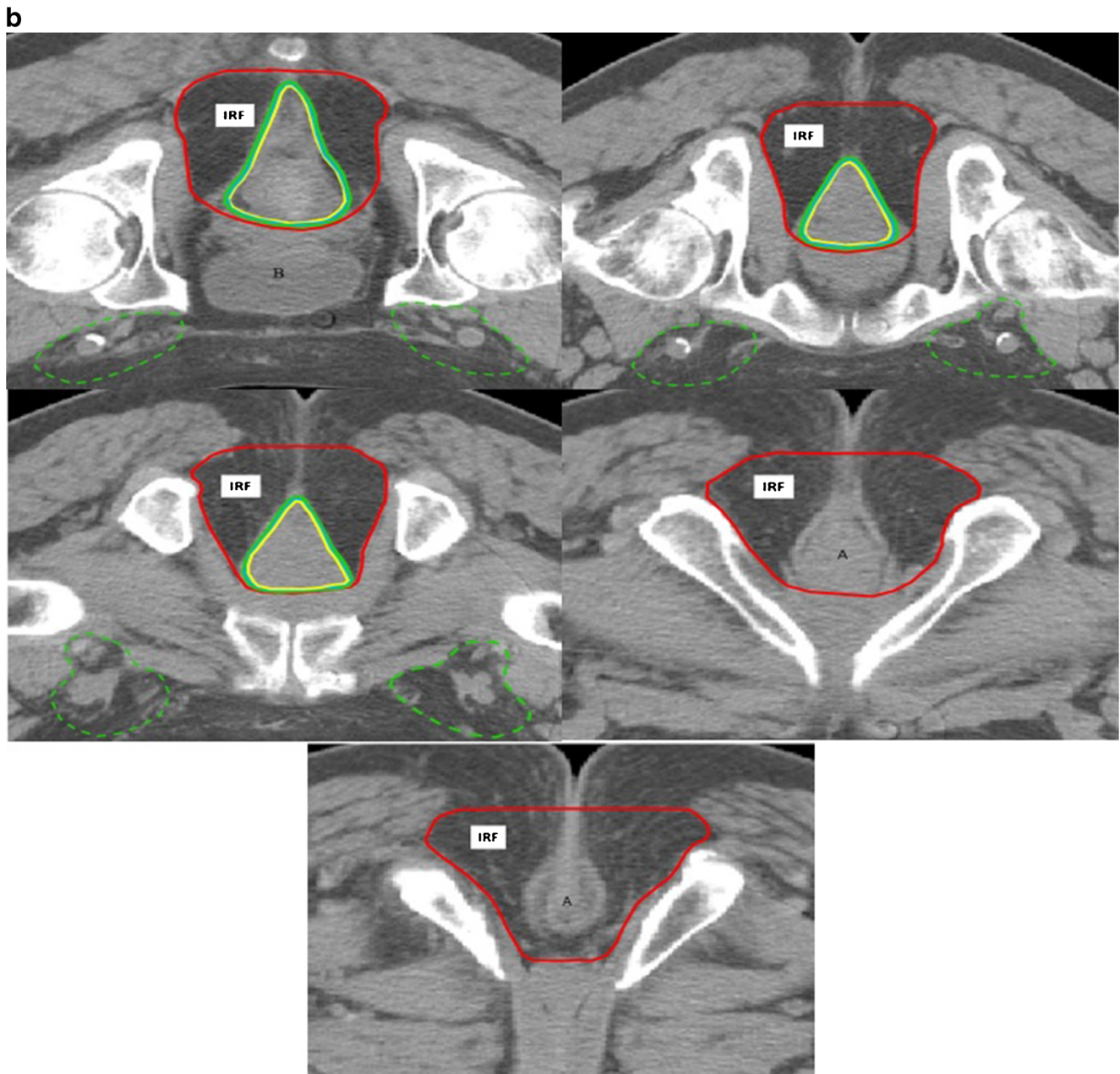
**Fig. 3 a, b** Definition of CTV on axial CT scans are shown: standard contouring (cT3 and/or  $N_{1-2} > 10$  cm above the anal canal) (yellow), expansions in case of ischio-rectal fossa invasion (red); expansion in tumors less than 10 cm from the anal margin (blue); expansion in case of anterior organs infiltration (green); expansion in case of other external

iliac lymph nodes involvement (green “dotted”), expansion in case of anal sphincter and/or the lower one third of the vagina involvement (green “dashed”). A anal canal, B bladder, EIV external iliac vessels, IIV internal iliac vessels, IRF ischio-rectal fossa, LDEI lateral-distal external iliac nodes area, OV obturator vessels

This criterion was further applied to distal external iliac nodes. These are usually excluded from CTV contouring of pelvic tumors but they should be included in case of external iliac node involvement or in case of inguinal node irradiation [18].

In case of (1) ischio-rectal invasion and (2) anal sphincter/lower third of the vagina involvement, the sphincter complex and ischio-rectal fossa were also included in the CTV. On the contrary, the recommendation

of Roels and colleagues to include ischio-rectal fossa also in patients undergoing anterior resection in RC located less than 6 cm from the anal verge was not followed [14]. In preoperative RT setting when an abdominoperineal resection is planned, we followed the recommendation of Valentini and coworkers to omit the inclusion of ischio-rectal fossa in tumors superficially infiltrating this area because of high risk of skin toxicity and delayed perineal wound healing [15•].



**Fig. 3** continued.

Finally, due to the risk of perineural spread in case of sacral infiltration, the sacral canal was included in the CTV of these patients.

Table 2 and Fig. 3a, b show CTV delineation in different clinical situations.

## Discussion

In our systematic analysis, current recommendations on CTV definition in preoperative RT of RC were reviewed. A limit of this analysis is that only information about

CTV definition was collected and reviewed. In clinical practice, radiotherapy planning also requires GTV definition particularly when a boost to macroscopic tumor is planned. Some indications about this issue were published by Gwynne S. and coworkers [19].

A large variability in available indications was observed, partly arising from differences in methods used in guidelines development. For example, Roels et al. guidelines [14] were derived from a systematic review on site of lymph node metastasis and of local recurrence after surgery. Instead, the RTOG Guidelines [12] were generated by *computer-generated consensus*.



The variability of different recommendations involved different aspects. For example, compared to other authors, Nijkamp et al. [13] proposed a cranial reduction of mesorectal and presacral space contouring on the basis of pelvic recurrence site in Dutch total mesorectal excision trial. The authors suggested that in patients without nodal and CRM involvement, the upper margin of the CTV may be lowered below the S2–S3 interspaces. This reduction is able to achieve a 60–80% reduction of small bowel irradiation. This evidence, already reported by Sik et al. [20] in a previous study on 99 RC local recurrences, could be useful especially in specific situations: the presence of a large volume of small bowel in the pelvis, previous pelvic RT, advanced age, and significant comorbidities. Even in a recent brief opinion by Joye and Haustermans [21], some adjustments of cranial border compared to previous guidelines [14] were suggested by shifting it at the level of superior rectal artery branching in multiple smaller vessels (S1–S2 interspaces) for tumors without involvement of mesorectal fascia and pelvic nodes on staging MRI. Based on post-TME era data on local recurrences [13, 20, 21], in order to reduce the small bowel exposure, Valentini et al. [15] recently proposed to lower the cranial level of lateral lymph node delineation (in case of cT3N0 tumors without invasion of the mesorectal fascia) at the same level of the cranial border of the mesorectum (corresponding to the bifurcation of the superior rectal artery).

Also, about CTV anterior margin definition, several variations were noted: (1) the RTOG guidelines [12] were more generous since they took into account the daily variability (organ motion) of anatomical structures in front of the rectum (e.g., bladder); (2) Roels and colleagues recommendations [14] used the ureters as an anatomical landmark to define the anterior margin of the lateral lymph node space; (3) Lorchel and coworkers [11] proposed to include only the mesorectum in the CTV; and (4) Valentini et al. [15] proposed a modification of the anterior border of lateral lymph node subsite, including the obturator lymph nodes, named as anterior lateral lymph nodes, by moving forward the anterior border behind the external iliac vessels, only in case of cT4 with anterior organ infiltration and/or cN2 and positive nodes in the posterior lateral lymph nodes.

Finally, even the inclusion of ischiorectal fossa in the CTV of patients with tumors less than 6 cm from the anal verge was discussed. In fact, this approach was criticized because relapses in this site are observed almost exclusively in patients undergoing abdominoperineal resection and because of the higher toxicity rate produced by including in CTV this subsite [22]. Valentini and coworkers [15] proposed the inclusion of ischiorectal fossa in CTV only when it is infiltrated by the tumor or if the tumor invades the external anal sphincter.

## Conclusion

In summary, the results of this analysis showed significant differences between CTV contouring guidelines of RC. Several studies highlighted the strong variability in target delineation of different tumors, particularly in gastrointestinal cancers [8, 23]. Based on the variations, the need of shared guidelines for CTV definition was stressed. However, our study clearly shows an underlying problem. Even in a very frequent cancer such as RC, where the role of adjuvant RT is widely established, there is no clear definition about what is the “standard” CTV. We could comment that this is not entirely a surprise. Only in recent decades it was understood that target of radical surgery is the whole mesorectum excision. Therefore, it is likely that radiation oncologists in different radiotherapy centers are irradiating different volumes. Obviously, this situation limits the reliability of outcome comparisons in terms of local control and treatment-related toxicity.

Therefore, this analysis highlights the need for further discussion and a first step to reduce these variations.

## Compliance with Ethical Standards

**Conflict of Interest** Marianna Nuzzo, Amalia Bisceglia, Milena Giordano, Lucia Giaccherini, Alessandra Guido, Gabriella Macchia, Annamaria Vinciguerra, Giovanna Mantello, Giuseppina Sallustio, Savino Cilla, Silvia Cammelli, Francesco Deodato, Milly Buwenge, Domenico Genovesi, Lorenzo Fuccio, and Alessio G. Morganti declare they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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