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Basic Original Report

International Consensus Guidelines for Adjuvant Radiation Therapy for Bladder Cancer After Radical Cystectomy: Update From an IBIS Workgroup

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Abstract

Purpose: In 2016, international consensus clinical target volume (CTV) guidelines for adjuvant radiation treatment after radical cystectomy in patients with muscle-invasive bladder cancer with high risk for locoregional failure (LRF) were published. A subsequent external validation study recommended several CTV optimizations (CTV-OPT). This study aimed to update international consensus guidelines based on new clinical experiences.

Methods and Materials: Phase 1 (delineation interobserver variability): Four observers delineated the CTV of 9 patients post radical cystectomy, as in clinical practice. Interobserver agreement in contouring was evaluated using volume- and κ-statistics. Phase 2 (pattern of failure analysis): Among a prospective cohort of 72 patients treated with adjuvant radiation treatment, 11 developed LRF (10 available for review). LRFs were mapped in predefined pelvic subsites (ie, common, external and internal iliac, obturator and presacral node

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regions, and cystectomy bed), and their distance to CTV-OPT was measured. The actual delivered dose at each relapse site was calculated. Phase 3 (review CTV): Based on the results of phase 1 and 2, 5 senior radiation-oncologists (International Bladder Investigator Society) reviewed the published CTV borders and provided an update when indicated.

Results: Phase 1: The mean overall κ-value was 0.66 (range, 0.60-0.70), indicating substantial overall agreement per Landis-Koch criteria. Specific κ-values per area indicated for the common iliac and obturator node regions only slight and moderate variability, respectively. Phase 2: Thirteen out of 16 LRFs centers were not included in the CTV-OPT. Ten LRF sites received a median dose <45 Gy, of which 6 were located in the cystectomy bed that was not included in the CTV because of negative radical cystectomy margins. Phase 3: Key recommendations by the panel were to include the entire common iliac node region and the cystectomy bed regardless of surgical margin status and a reaffirmation to not crop the CTV out of bowel.

Conclusions: International consensus guidelines were updated.

Introduction

Most patients with muscle-invasive bladder cancer (MIBC) are treated with neo-adjuvant chemotherapy followed by radical cystectomy (RC) and pelvic lymph node dissection.[1] Still, up to 40% of patients with more advanced disease stage develop locoregional failure (LRF), which is associated with a poor survival.[2,3] A study from the 1980s suggested that adjuvant radiation treatment (ART) reduces LRF but also induces significant toxicity.[4] In the meantime, prospective trials, using modern radiation therapy techniques, have re-evaluated the safety and efficacy of ART in MIBC patients at high risk for developing LRF.[5] These trials suggested that ART is safe and effective.[6,7] To guide the contouring of the clinical target volume (CTV) for ART in these high-risk MIBC patients after RC, in 2016, international consensus CTV (CTV-IC-2016) guidelines were published by Baumann et al.[8] After external validation, Reddy et al[9] proposed an optimized CTV (CTV-OPT). The aim of this study was to develop updated international consensus CTV guidelines by evaluating the current contouring practice that makes use of existing guidelines and the locoregional ART results.

Methods and Materials

This study consisted of 3 consecutive phases. In the first phase, the interobserver variability in CTV delineation practice was assessed to identify areas of high interobserver variability. In the second phase, the pattern of LRF after ART was mapped and analyzed with regard to the CTV-OPT.[9] In the final phase, the previously published CTV borders[8,9] were reviewed and updated by an expert panel, based on the results gathered in the previous phases.

Phase 1: Delineation interobserver variability

Ten patients referred for ART after RC were selected for retrospective delineation of the CTV. Four radiation oncologists (PS, VM, PD and VF) from as many different institutions, with special interest in ART in bladder cancer, took part as observers in the delineation process. The observers were asked to delineate the appropriate CTV, as they would do in clinical practice. Therefore, the observers received all relevant clinical information to guide their delineation (ie, age, medical history, tumor, nodes, metastases status [pre- and post-RC], tumor localization, neoadjuvant chemotherapy status, number of removed and positive lymph nodes, resection margin status, and histology). Delineation of the CTV was done on the patient's anonymized planning CT. All planning CTs were performed in supine position with a 3- or 5-mm slice thickness from the inferior aspect of the lung until mid-femur, 5 to 10 weeks after the RC. The observers were blinded to each other's contoured CTVs. The contoured CTVs of 1 patient could not be analyzed due to missing 1 observer's CTV.

Statistical considerations

The CTV contours were analyzed using the Computational Environment for Radiation therapy Research, an open-source MATLAB-based radiation therapy planning analysis software.[10] Within each patient, the volumes of the contoured CTVs were compared by evaluating their mean, minimum, and maximum volume. Also, the intersection volume (ie, area of total agreement between the observers) and the union volume (ie, largest volume created by using the outermost delineated contours) were constructed and compared. Furthermore, the mean level of interobserver agreement corrected for chance was calculated using generalized κ-statistics.[11] According to Landis and Koch criteria,[12] the following labels were assigned to the corresponding ranges of κ to represent the strength of interobserver agreement: poor (<0.00), slight (0.00-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and almost perfect (0.81-1.00). In addition to the overall κ calculation, 4 consecutive areas were marked on the planning CTs, and their specific κ-value was calculated to identify more specific areas of variability. The anatomic boundaries of the 4 areas were marked by horizontal planes, based on the published CTV borders.[8,9] From cranial to caudal: areas 0, 1, 2, and 3 were separated from each other by the lumbosacral joint, the superior aspect of the femoral head, and the superior aspect

of the pubic symphysis, respectively. Area 0 included only the common iliac lymph node (CI) region. Area 1 contained the external iliac (EI), internal iliac (II), presacral (PS), and part of the obturator (OR) lymph node regions. Area 2 contained a major part of the OR and when included, part of the cystectomy bed (CB). Area 3 only contained the CB (if delineated). Visual representation of pelvic lymph node regions and their relation to the different analyzed areas can be found in Supplementary Materials.

Phase 2: Pattern of failure analysis

Between August 2014 and October 2020, 72 patients with MIBC were treated with ART after RC within a Belgian prospective phase 2 trial.[7] Within this trial, all patients received elective pelvic nodal irradiation using intensity modulated arc therapy. The lymph node areas located along the common, internal and external iliac artery, obturator fossa, and presacral were delineated. Using an isotropic expansion of 5 and 12 mm around the delineated lymph nodes, a CTV and planning target volume were constructed, respectively. In case of a positive resection margin, the CB was included in the radiation field. A median dose of 50 Gy delivered in 25 fractions, 5 times a week, was prescribed to the planning target volume ± CB. Daily cone beam CT was used. After a median follow-up time of 18 months (range, 1-72 months), 11 patients (15%) developed LRF,[7] defined as any recurrence in the pelvic lymph nodes or soft tissues below the aortic bifurcation up to and including the cystectomy bed. Due to missing imaging for 1 patient, 10 patients (with 16 locally recurrent masses) were analyzed. The LRFs of each patient were mapped on their ART planning computed tomography (CT), as seen on the first imaging study showing the relapse. Blood vessels and bone structures were used as reference points in the mapping process. The center of the relapse volume was determined by the treatment planning system (ie, Raystation; RaySearch Laboratories). The LRFs were allocated in 1 of 6 predefined pelvic lymph node regions (ie, CI, EI, II, OR, and PS regions, and the CB). Allocation was mainly based on the location of the center of the LRF, but it could be altered by clinical information (ie, surgical report and imaging). Relapses that were located at the edge of the radiation therapy field and could not be categorized in 1 of the 6 predefined pelvic lymph node regions were categorized as "other." For each patient, the CTV-OPT, as proposed by Reddy et al,[9] was delineated on their planning CT. Thereafter, we examined whether the location of the relapse site center would have been covered by the CTV-OPT. Actual delivered dose at all relapse sites was calculated by the treatment planning system, to confirm whether adequate dosage was administered (ie, ≥45 Gy; 90% of the prescribed D50 of 50 Gy). Furthermore, the distance between the center of the LRFs located in the predefined pelvic regions and the nearest CTV-OPT contour was measured.

Phase 3: Review of the delineation guidelines

Guided by the results of phase 1 and 2, an expert panel systematically re-evaluated the published CTV border recommendations for each pelvic region[8,9] in an online forum until an updated consensus was reached. The panel consisted of 5 genitourinary radiation oncologists (PS, JPC, BCB, VM and VF) from the International Bladder Investigator Society representing 4 different countries.

Results

Phase 1: Delineation interobserver variability

The CTV and κ-statistics are presented in Table 1. The mean union volume (±standard deviation) was 743.4 (± 67.4) mL. However, the mean intersection volume (±standard deviation) was only 234.4 (± 26.4) mL. The mean overall κ-value was 0.66 (range, 0.60-0.70), indicating substantial overall agreement between the observers. The mean specific κ-values for area 0, 1, 2, and 3 were 0.10, 0.72, 0.52, and 0.72, respectively. Examples of the variation in CTV delineation are shown in Fig. 1.

Phase 2: Pattern of failure analysis

In the cohort of 72 patients, 8 out of 58 patients with a negative resection margin and 3 out of 14 patients with a positive resection margin developed LRF. A total of 16 LRFs spread across 10 patients were identified and mapped (Fig. 2). A summary of these 10 patients' characteristics can be found in Supplementary Materials. Of the 16 LRFs, 11 could be categorized in the predefined pelvic regions (1 OR, 2 PS, 2 II, 6 CB). Five LRFs were categorized as "other," of which 4 consisted of a mesenteric, peritoneal, ureter, and implantation (abdominal trocar) failure. One relapse located at the level of the inguinal canal was a borderline LRF but ultimately was categorized as "other" due to its presumed spread from a surgical clip located just anterior-inferior to the radiation therapy field covering the EI nodes. The location of the LRFs and their coverage status by the CTV-OPT are summarized in Table 2. The radiation dose at the CTV-OPT excluding relapse sites was calculated; 10 out of the 13 sites had a median dose <45 Gy (range, 17.25-43.87 Gy). Six out of these 10 underdosed sites were located in the CB. In case the CB would have been treated in the patients with a negative resection margin, the CTV-OPT would have included all 6 sites. A detailed overview of the dose

Table 1 Interobserver variability: Summary volume and κ statistics

	Volume			κ[†]				
	Mean volume (range)	Intersection volume	Union volume	Overall κ	Area 0 κ	Area 1 κ	Area 2 κ	Area 3 κ
Patient 1[*]	572.9 (487.3-692.6)	294.2	972.2	0.65	0.11 (3)	0.65 (4)	0.62 (4)	0.79 (4)
patient 2	230.6 (183.5-282.4)	109.1	418.0	0.60	-0.04 (2)	0.70 (4)	0.33 (4)	- (0)
patient 3[*]	465.4 (382.9-520.9)	234.4	790.9	0.63	-0.02 (2)	0.64 (4)	0.64 (4)	0.68 (4)
patient 4[*]	701.0 (658.1-764.2)	396.6	1045.7	0.70	0.10 (2)	0.71 (4)	0.58 (4)	0.70 (4)
patient 5	498.6 (442.5-570.3)	274.4	776.2	0.69	0.41 (3)	0.77 (4)	0.50 (4)	- (1)
patient 6	453.4 (355.3-569.0)	256.4	743.4	0.67	- (1)	0.74 (4)	0.47 (4)	- (1)
patient 7	341.7 (275.0-385.2)	199.5	530.8	0.70	- (1)	0.77 (4)	0.56 (4)	- (1)
patient 8	377.9 (304.3-424.8)	223.3	588.4	0.70	- (1)	0.77 (4)	0.51 (4)	- (1)
patient 9	383.7 (285.1-457.3)	193.9	656.3	0.64	0.04 (2)	0.73 (4)	0.49 (4)	- (1)

[*] Patients with a positive resection margin.
[†] The numbers in parentheses represent the number of observers that delineated part of the clinical target volume in the indicated area.

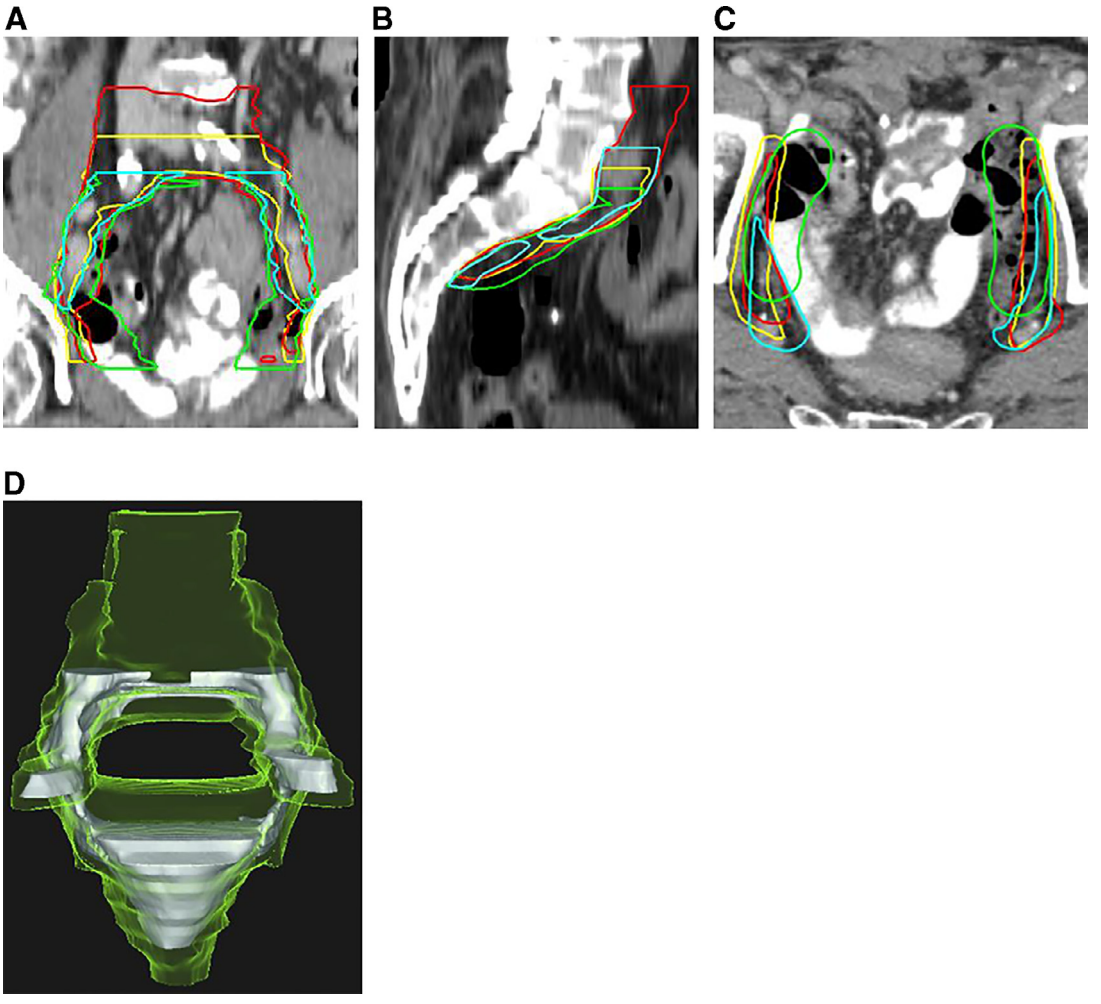

Figure 1 Interobserver variability in clinical target volume delineation. Different delineated clinical target volumes for patient 2 (overall κ, 0.60; cystectomy bed excluded) in coronal, A, sagittal, B, and axial, C, view, respectively. Each observer is assigned a different color. D, Three-dimensional structure of the clinical target volumes intersection volume (white) and union volume (green) of patient 1 (overall κ, 0.65; cystectomy bed included).

distribution at the LRF sites is presented in Supplementary Materials. The distance between the 11 LRFs, in the predefined pelvic regions, and the nearest CTV-OPT border is shown in Table 3.

Phase 3: Review of the delineation guidelines

The CTV borders of each pelvic lymph node region and the CB were systematically reviewed (as described in the following sections). The updated CTV borders are described in Table 4.

CB

The interobserver variability assessment in phase 1 showed that all observers agreed to include and exclude the CB in case of a positive and negative resection margin, respectively, suggesting good uptake of the existing consensus guidelines. The CB region was mainly located in area 3, in which substantial agreement was indicated (κ = 0.72). In the pattern of failure analysis, 5 out of 10 patients with LRF had at least 1 relapse at the level of the CB. These 5 patients all had a negative resection margin and so the CB was not included in the CTV, as stated in the CTV-IC-2016 guidelines.[8] If the CB would have been included, all CB relapses would have been located within the CTV-OPT borders. Similarly, in the pattern of failure analysis by Murthy et al,[13] a high CB recurrence rate was reported after RC in spite of a low resection margin positivity rate. Furthermore, none of the 14 patients with a positive resection margin (which lead to CB inclusion in the CTV) showed a failure at the level of the CB after ART. In the randomized phase II trial by Zaghloul et al[6] for patients with margin-negative locally advanced disease, adjuvant chemoradiation therapy with treatment of the CB and regional nodes for all patients resulted in 96% 2-year local-regional control, suggesting that routine inclusion of the CB is

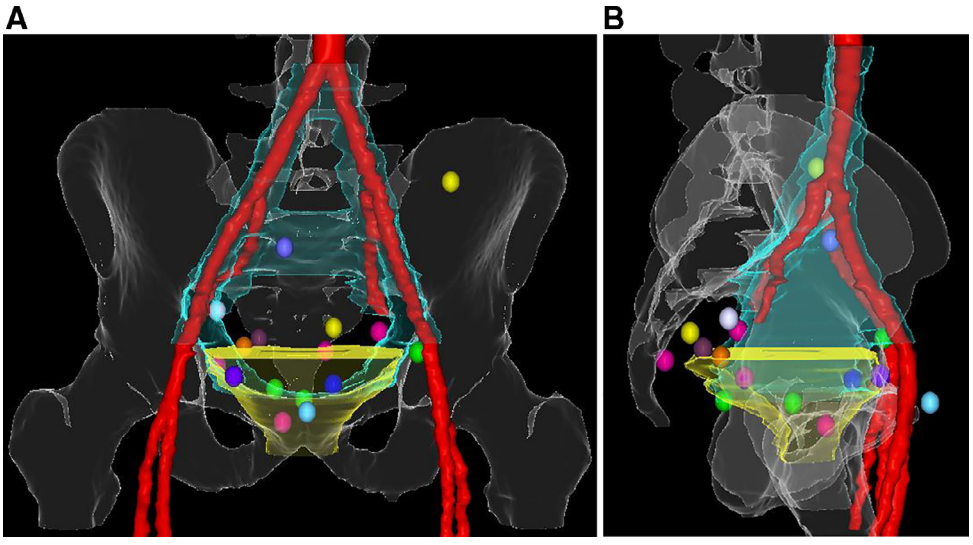

Figure 2 Three-dimensional overview images of the locoregional failure sites. Coronal, A, and sagittal, B, view of the locoregional failure sites. The failure sites are mapped as spheroids using an isometric expansion of 10 mm from the center of the on-imaging visible relapse volume. Each patient is depicted by a different color. The optimized consensus clinical target volume (as proposed by Reddy et al[9]) is shown, lymph node regions (blue) and cystectomy bed (yellow). Arterial blood vessels and bony anatomy are displayed as the reference points.

important. Based on these findings, the panel recommended inclusion of the CB in the CTV in all patients (regardless of resection margin status). In addition, in light of recent ART trials with modern radiation therapy techniques showing that treatment is well tolerated even when the CB is included,[6,7] the panel felt that the CTV should not be cropped off of bowel within this region.

Iliac nodes

The common iliac nodal region was located in area 0, in which there was only slight interobserver agreement (κ = 0.10). Visual inspection showed that the variability was largely due to the difference in superior border of the iliac nodes. Only 1 observer included the CI region up to the aorta bifurcation. In all 72 patients who underwent ART, the CI region was included (up to the aorta bifurcation) in the CTV. No LRFs were observed in the CI region, while Reddy et al[9] reported 25% of the LRFs after RC in this region. Based on these findings, the panel recommended including the CI region in the CTV, as previously suggested by Reddy et al[9] (ie, CTV-OPT). This recommendation is consistent with the NRG Oncology guidelines for nodal contouring of prostate cancer[14] and the postoperative NRG Oncology/Radiation Therapy

Table 2 Location of LRF sites with respect to CTV-OPT

Region	Failures outside CTV-OPT /total LRF	Patients with failures outside CTV-OPT/total patients
Common iliac	0/0 (-)	0/10 (0%)
external iliac	0/0 (-)	0/10 (0%)
internal iliac	0/2 (0%)	0/10 (0%)
obturator	0/1 (0%)	0/10 (0%)
presacral	2/2 (100%)	2/10 (20%)
cystectomy bed		
-excluded in R0*	6/6 (100%)	5/10 (50%)
-included in R0†	0/6 (0%)	0/10 (0%)
other	5/5 (100%)	5/10 (50%)
total		
-CB excluded in R0*	13/16 (85%)	9/10 (90%)
-CB included in R0†	7/16 (44%)	6/10 (60%)

Abbreviations: CB = cystectomy bed; CTV-OPT = optimized clinical target volume; LRF = locoregional failures; R0 = negative resection margin.
* In all patients with a CB failure, the CB was excluded from CTV-OPT because of their R0 status.
† In case the CB is included in all patients (regardless of margin status), all LRF sites would have been included in CTV-OPT.

Table 3 Distance between the locoregional sites and the CTV-OPT in cm, excluding "other" LRF

	LRF site	CI	EI	II	OR	PS	CB*
Patient 1	Lesion 1	-	-	-	-	-	0
	Lesion 2	-	-	-	-	-	-
	Lesion 3	-	-	-	-	-	0
Patient 2	Lesion 1	-	-	-	-	-	0
Patient 3	Lesion 1	-	-	-	-	-	0
Patient 4	Lesion 1	-	-	-	-	-	-
Patient 5	Lesion 1	-	-	-	-	-	-
	Lesion 2	-	-	-	-	5.75†	-
Patient 6	Lesion 1	-	-	0	-	-	-
Patient 7	Lesion 1	-	-	-	-	-	-
Patient 8	Lesion 1	-	-	-	-	-	0
Patient 9	Lesion 1	-	-	-	-	-	-
Patient 10	Lesion 1	-	-	-	0	-	-
	Lesion 2	-	-	-	-	4.00†	-
	Lesion 3	-	-	-	-	-	0
	Lesion 4	-	-	0	-	-	-

Abbreviations: CB = cystectomy bed; CI = common iliac nodes; CTV-OPT = optimized clinical target volume; EI = external iliac nodes; II = internal iliac nodes; LRF = locoregional failures; OR = obturator nodes; PS = presacral nodes.

* In all 5 patients with a CB failure, the CB wasn't included in the CTV-OPT because of their negative resection margin status.

† Both relapse sites are located inferior to the CTV-OPT.

Oncology Group guidelines for endometrial and cervical cancer.[15] The EI and II nodal regions were located in area 1, in which substantial interobserver agreement was indicated ($\kappa = 0.72$). In the EI region, no LRFs were diagnosed after ART. In the II region, 2 LRFs were observed. Both LRFs were included in the CTV-OPT. Dose calculation confirmed that both LRF sites were adequately covered. Based on these results, no adjustments to the CTV-IC-2016 guidelines[8] for the EI and II node regions were proposed.

OR

The obturator region was mainly located in area 2, in which moderate interobserver agreement was found ($\kappa = 0.52$). Visual inspection showed that the variability was largely due to variation in the medial border of the OR. Some observers adapted their contours by excluding bowel loops while others did not. To a lesser degree, differences in anterior and posterior borders were also noted. Only 1 LRF was observed in the OR region. The LRF site was included in the CTV-OPT. Dose calculation at the LRF site confirmed an adequate dose was delivered. Due to the limited gastrointestinal toxicity reported in recent ART trials,[6,7] the panel felt that it is not necessary to crop the CTV-IC out of the bowel, as already stated in the CTV-IC-2016 guidelines.[8] In the CTV-IC-2016 guidelines, the anterior and posterior border of the ilium were used as borders (horizontal plane) of the OR. The panel changed these to the anterior and posterior edge of the obturator internus muscle, respectively. This recommendation is consistent with the NRG Oncology guideline for prostate cancer.[14]

PS

The presacral region was located in area 1, in which substantial interobserver agreement was indicated ($\kappa = 0.72$). Two out of 16 LRFs were located in the PS region. Both LRFs were located outside the CTV-OPT borders (4 and 5.75 cm to inferior at the level of S4 and S5, respectively). Dose calculation confirmed that both LRF sites were inadequately covered. The panel felt that the CTV adaptations needed to include both LRF sites were too extensive to be recommended. However, the panel proposed to lower the inferior PS border to the bottom of S3. This mirrors the inferior PS border described in the NRG-Oncology guidelines for prostate cancer.[14]

Clinical adaptations

Due to a relapse that presumably spread from a surgical clip located at the margin of the radiation therapy field, the panel highlighted the importance of using clinical information (eg, surgery and pathology reports) to guide the delineation process. A more extensive CTV may be preferable to include surgical clips or in the case of extranodal tumor involvement. This is at the discretion of the radiation oncologist.

Table 4 International Bladder Investigator Society updated international consensus clinical target volume definition

	Superior	Inferior	Anterior	Posterior	Lateral
Presacral nodes	Lumbosacral joint (L5-S1)	Inferior aspect of S3	1-1.5-cm anterior to sacrum	Sacrum	Right and left common iliac vessels
Iliac nodes	Iliac vessels from bifurcation of the abdominal aorta	External iliac: superior aspect of femoral heads Internal iliac: point of exit through greater sciatic notch or no longer visible on CT	7-mm expansion around iliac vessels		
Obturator nodes	Bifurcation of common iliac vessels	Superior aspect of pubic symphysis	Anterior edge obturator internus muscle	Posterior edge obturator internus muscle	1.9-cm medial to obturator internus muscle (no cropping to the bowel)
Cystectomy bed	2-cm above superior aspect of pubic symphysis	Male patients: 2-3 mm superior to penile bulb. Female patients: 1 cm below inferior pole of obturator foramen	Posterior aspect of pubic symphysis and planes extending superiorly and inferiorly from posterior aspect of pubic symphysis	Anterior one-third aspect of anorectal circumference and plane extending superiorly from anterior border of rectum	Medial border of obturator internus muscle and prostate bed or vaginal wall

Abbreviation: CT = computed tomography.

Discussion

Radiation treatment for MIBC patients with high risk of LRF after RC needs to be reconsidered after the publication of recent trials that suggest that ART is safe and effective. Current contouring guidelines for ART are based on relapse sites after RC.[8,9] The current study evaluated the variability in CTV contouring and assessed the sites of relapse after ART post-RC in clinical practice. Review by an expert panel resulted in the formulation of updated IC guidelines for ART after RC in pathologic high-risk MIBC. To our knowledge, this study also provides the first pattern of failure analysis after ART in bladder cancer. Several points may be discussed. In the first phase of our study, the observers were not explicitly asked to delineate the CTVs according to the CTV-IC-2016 guidelines,[8] although most observers indicated that they followed the consensus guidelines. Thus, this study does not evaluate the reproducibility of the CTV-IC-2016 language, but rather the implementation of these guidelines in clinical practice. By dividing the CTV into 4 predefined areas, a more targeted analysis of each pelvic lymph node region is possible. However, the presence of more than 1 lymph node region in some areas limits a fully targeted variability analysis. The results of the pattern of failure analysis are based on the results of a single, but multicentric, prospective study.[7] All radiographical LRFs were included, and pathologic confirmation was not required. The risk of overdiagnosis is limited by evaluating sequential imaging. The risk of underreporting LRFs is minimized by CT imaging that is performed at regular intervals, according to the study protocol.[7] All LRFs were diagnosed with diagnostic CT or magnetic resonance imaging (hollow tabletop), while mapping was done on the planning CT images (flat table top). Because we are using the blood vessels as the main reference point, we expect this to have only a limited effect on the accuracy of the mapping. Assignment of the LRF to 1 of the pelvic regions and determination of its distance to the CTV-OPT contour are based on the center of the relapse volume. Nonuniform tumor growth could potentially affect the classification (pelvic regions) and measurement (distance LRF to CTV-IC) process. We tried to minimize the risk of misclassification by considering clinical information in the allocation process. We chose to measure the distance between the LRFs and the CTV-OPT because it

incorporated patterns of failure findings within an additional surgical series, compared with the CTV-IC-2016, and was similar to the CTV in the ART trial. However, the CTV used in the ART trial and the CTV-OPT did not have identical borders. To account for this, the CTV-OPT was delineated for each patient and the actual delivered dose at the relapse sites was calculated. This way, it can be confirmed whether relapse sites in or out of the CTV-OPT received an (in)adequate dose. Furthermore, the proposed CTV adaptations are based on the recommendations of a selected panel of experts. To further improve consistency within the field of radiation therapy generally, the panel harmonized their CTV recommendations with the postoperative delineation guidelines for prostate cancer[14] and for endometrial and cervical cancer,[15] when feasible. The results of the current study can further guide the CTV contouring practice in other ART trials. The LRF results of these trials are essential to validate our updated CTV consensus guidelines.

Conclusions

The current contouring practice and locoregional pattern of failure after ART were evaluated. Based on the results of these evaluations, an expert panel updated the IC CTV guidelines. Key recommendations by the panel were to include the CI region, the CB regardless of margin status, and to not crop the CTV to the bowel.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2022.05.014.

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