Radiotherapy and Oncology 133 (2019) 20–27

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic Review

A systematic review and meta-analysis of pT2 rectal cancer spread and recurrence pattern: Implications for target design in radiation therapy for organ preservation

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ARTICLE INFO

Article history:
Received 3 November 2018
Received in revised form 20 December 2018
Accepted 21 December 2018
Available online 14 January 2019

Keywords:
Rectal cancer
Clinical target volume
Organ-preserving treatment

ABSTRACT

Background: There are no guidelines on clinical target volume (CTV) delineation for cT2 rectal cancer treated with organ preservation.
Materials and methods: A systematic review and meta-analysis were performed to determine the extent of distal mesorectal (DMS) and distal intramural spread (DIS), the risk of lateral lymph node (LLN) metastases in pT2 tumours, and regional recurrence pattern after organ preservation.
Results: The rate of DMS > 1 cm was 1.9% (95% CI: 0.4–5.4%), maximum extent: 1.3 cm. The rate of DIS > 0.5 cm was 4.7% (95% CI: 1.3–11.5%), maximum extent: 0.8 cm. The rate of LLN metastases was 8.2% (95% CI: 6.7–9.9%) for tumours below or at peritoneal reflexion and 0% for higher tumours. Regional nodal recurrences alone were recorded in 1.0% (95% CI: 0.5–1.7%) of patients after watch-and-wait and in 2.1% (95% CI: 1.2–3.4%) after preoperative radiotherapy and local excision. Thus, the following rules for CTV delineation are proposed: caudal border 1.5 cm from the tumour to account for DMS or 1 cm to account for DIS, whichever is more caudal; cranial border at S2/S3 interspace; inclusion of LLN for tumours at or below peritoneal reflexion. A planning study was performed in eight patients to compare dose–volume parameters obtained using these rules to that obtained using current guidelines for advanced cancers. The proposed rules led to a mean 18% relative reduction of planning target volume, which resulted in better sparing of organs-at-risk.
Conclusion: This meta-analysis suggests a smaller CTV for cT2 tumours than the current guidelines designed for advanced cancers.

Two main approaches are used for organ preservation in rectal cancer: i.e., accidental and intentional. The accidental approach (i.e., pick the winners) uses routine preoperative radiotherapy for patients with advanced tumour before planned total mesorectal excision (TME). Those with favourable tumour response are then observed without TME or undergo full-thickness local excision [1–3]. The intentional approach uses irradiation for organ preservation, in patients who otherwise do not require preoperative radiotherapy [1,4,5]. This approach is used mostly in patients with low cT2 cancers.

There are no published guidelines on clinical target volume (CTV) delineation specific for cT2 tumours where organ preservation is an issue. Therefore, existing guidelines designed for preoperative radiotherapy of advanced tumours are being used [6,7]. These guidelines propose a large CTV volume containing the mesorectum and pelvic nodal basin, starting from the sacral promontory down to the puborectalis muscle. Such a large volume has been questioned for early rectal cancer [8,9] because most patients will be node-negative and the extent of intramural and mesorectal spread is supposed to be limited to the immediate proximity of the primary tumour. Smaller and personalized CTV adjusted to the tumour stage and location may decrease toxicity without compromising oncological outcomes. Decisions on which areas should be included in the CTV must be evidence-based. This evidence must reflect both a pattern of cancer subclinical spread and a pattern of local recurrence after organ-preserving treatment. Thus, we performed a systematic review and meta-analysis to determine the extent of distal mesorectal (DMS) and distal intramural spread (DIS) in pT2 tumours and to establish whether a risk of upward lymphatic spread and incidence of lateral lymph node

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https://doi.org/10.1016/j.radonc.2018.12.024
0167-8140/

(LLN) metastases in pT2 tumours justifies inclusion of these areas into the CTV. According to the Japanese classification [10], we defined upward lymphatic spread as being that along superior rectal and inferior mesorectal vessels up to the root of the inferior mesorectal artery (approximate bony landmarks are between the S2/S3 interspace and L3). Next, we performed a systematic review of a pattern of locoregional recurrence after organ-preserving treatment, to establish a risk of recurrence in lymph nodes above the sacral promontory (i.e. above the commonly used cranial CTV border), that are untouched by surgery when organ preserving treatment is used. Following the results of this review, we aimed to create a proposition of the rules for CTV delineation for organ preservation in cT2 disease and to perform a planning study to compare dose–volume parameters obtained using the proposed rules with that obtained using the current guidelines [6,7].

Materials and methods

A protocol for the study was not written. Only the aims were predefined as outlined in the Introduction. Original studies qualified for the systematic review and meta-analysis if they reported an unselected group of patients with pT2 tumours treated with radical surgery without preoperative irradiation and any of the following: (i) the distance of the metastatic lymph nodes and/or extranodal deposits caudally from the tumour border; (ii) the rate of patients with upward lymphatic spread; (iii) the length of intramural spread caudally from the tumour border; (iv) the rate of patients with LLN metastases with respect to the tumour localization above or below peritoneal reflection. LLN were defined according to the Japanese classification, as internal illiac and obturator lymph nodes. Additionally, we evaluated the rate of patients with regional nodal recurrence after radiotherapy used for organ preservation. Only English-language studies were included. Articles were identified by a search of the PubMed database starting in 1982 (the beginning of the TME era) until September 2018 with the following keywords: (i) "rectal cancer" and "distal mesorectal spread"; (ii) "rectal cancer" and "proximal lymphatic spread" or "upward lymphatic spread"; (iii) "rectal cancer" and "distal intramural spread"; (iv) "rectal cancer" and "lymph nodes distribution" or "lateral nodes"; (v) "rectal cancer" and "watch-and-wait", or "non-operative management" or "organ preservation"; (vi) "rectal cancer" and "local excision" The computerized search was supplemented with manual searches of the reference lists and cross-referencing. Case reports or articles presenting results of palliative treatment were excluded. Full texts of all pertinent studies were obtained.

One of the authors (JS) performed the literature search. The data from relevant articles were independently extracted by the two authors (JS, KB). Disagreements were resolved by a consensus. In the event of multiple publications of overlapping patients' data, we included only the most recent report. The following data were extracted: study design (prospective or retrospective); number of patients; adjustment of measurements for tissue shrinkage after fixation (yes or no); the method of lymph nodes retrieval (i.e., conventional or fat clearing); number and rate of patients with metastatic nodes and extranodal deposits >1 cm, >1.5 cm and >2 cm caudally from the tumour border and maximum extent of this spread; number and rate of patients with upward lymphatic spread; number and rate of patients with intramural spread >0.5 cm and >1 cm caudally from the tumour border and maximum length of this spread; number and rate of patients with LLN metastases in tumours below or above peritoneal reflection; and number and rate of patients with regional nodal recurrences without concomitant intramural recurrences as well as the locations of these recurrences.

CTV planning study

Planning computed tomography (CT) scans of eight consecutive patients with cT2 disease who had already received radiotherapy for organ preservation were retrieved. Patients were scanned without intravenous and small bowel contrast in supine position using full bladder protocol. Diagnostic pelvic magnetic resonance (MR) images were co-registered. The following organs-at-risk were delineated: small bowel (peritoneal cavity), anal canal and vagina or penis bulb and testicles. Two CTV delineations were performed by the same physician for all patients: i.e., $CTV_{standard}$ according to the official guidelines [6,7] and $CTV_{proposed}$ according to the rules suggested by our meta-analysis. Uniform 1 cm margins were added to both CTVs to create planning target volumes (PTVs). Next, two treatment plans were performed by the same physicist for $PTV_{standard}$ and $PTV_{proposed}$ using a volumetric modulated arc therapy technique with 6 MV photon, for a total 50 Gy dose in 2 Gy fractions. PTVs and dose–volume parameters in the organs-at-risk were extracted and compared between the proposed and standard approaches.

Statistical methods

The pooled weighted rates were estimated using a meta-analytic approach with MedCalc statistical software (MedCalc Software, Ostend, Belgium). Inter-study heterogeneity was tested by Cochrane's Q (χ^2) assuming $p < 0.10$ is statistically significant and quantified with I^2 statistics. A fixed model was used for data sets with insignificant heterogeneity and a random model for those with significant heterogeneity.

Results

Search results

The majority (69.6%) of the relevant articles on nodal and intramural spread came from Japan because preoperative radiochemotherapy is rarely given in this country, lymph nodes found at each station in surgery are routinely labelled and sent separately for pathological assessment, and the lateral nodes are resected routinely.

Distal mesorectal spread

Nine relevant references that included 149 patients in total were identified (Table 1, Supplementary Figs. 1, 2) [11–19]. Cancer spread was reported as direct infiltration, lymph node metastases, vessel invasion, perineural invasion, lymphatic permeation and isolated foci in three reports and as spread only in lymph nodes in six reports. The pooled weighted rate of patients with any DMS was 5.7% (95% confidence interval [CI]: 1.0–13.8%). The pooled weighted rate of patients with DMS longer than 1 cm was 1.9% (95% CI: 0.4–5.4%). The maximum extent of spread was 1.3 cm.

Upward lymphatic spread

Relevant data were found in two articles that included 252 patients in total [22,23]. The pooled weighted rate of the upward spread was 5.0% (95% CI: 2.6–8.4%) for all patients (Table 2, Supplementary Figs. 3, 4). This rate was 6.0% for the subgroup of 181 patients with tumours below peritoneal reflection (95% CI: 3.0–10.4%).

Table 1
Distal mesorectal spread in patients with pT2 disease treated with surgery without preoperative radiotherapy.

	Design	Total number of patients	DMS > 1 cm below distal tumour border (%)	DMS of any extent (%)	Maximum extent of DMS (cm)	Clearing method[#]	Adjustment for shrinkage[&]
Koh [11]	P	9	0 (0)	0 (0)	0	No	NG
Yegen [12]	P	2	0 (0)	0 (0)	0	No	NG
Zheng [13]	P	16	0 (0)	0 (0)	0	LNRS[*]	NG
Morikawa [14]	P	27	0 (0)	5 (18.5)	0	Yes	No, cork board
Zhao [15]	P	11	2 (18.2)	4 (36.4)	1.3	No	Yes
Ono [16]	P	7	0 (0)	0 (0)	0	No	Yes
Reynolds [17]	P	6	0 (0)	0 (0)	0	No	No, cork board
Hida [18]	R	38	0 (0)	0 (0)	0	Yes	No
Yu [19]	P	33	0 (0)	0 (0)	0	No	No, cork board
Total number		149	2 (1.3)	9 (6.0)			
Pooled rate (95% confidence interval)			1.9% (0.4–5.4)	5.7% (1.0–13.8)			
Heterogeneity			χ^2 = 7.0, df = 8, p = 0.5, I^2 = 0.0%	χ^2 = 22.0, df = 8, p = 0.005, I^2 = 63.7%			

Abbreviations: DMS, distal mesorectal spread; NG, not given; P, prospective, R, retrospective.
[#] In the fat clearing method, the specimen was defatted with acetone and cleared with xylene. This method results in more than 50 nodes retrieval per patient.
[*] The lymph node revealing solution introduced by Koren et al. [20] was used to facilitate the identification of lymph nodes in the mesorectum.
[&] Adjustment for shrinkage: i.e., "yes" if reported distances were adjusted for tissue shrinkage and the shrinkage ratio was given or "cork board" if the fresh specimen was straightened and pinned on a cork board, which was supposed to give negligible shrinkage [21].

Table 2
Upward lymphatic spread (defined as that along superior rectal and inferior mesorectal vessels) in patients with pT2 disease treated with surgery without preoperative radiotherapy.

	Design	Number of patients (%)						
		Total	With upward spread	Lower rectum[*]		Upper rectum[*]	
				Subtotal	With upward spread	Subtotal	With upward spread
Hojo [22]	R	82	6 (7.3)	62	4 (6.5)	20	2 (10.0)
Kanemitsu [23]	P	170	6 (3.5)	119	6 (5.0)	51	0 (0)
Total number		252	12 (4.8)	181	10 (5.5)	71	2 (2.8)
Pooled rate (95% confidence interval)			5.0% (2.6–8.4)		6.0% (3.0–10.4)		2.2% (0.2–8.8)
Heterogeneity			χ^2 = 1.7, df = 1, p = 0.2, I^2 = 41.4%		χ^2 = 0.2, df = 1, p = 0.6, I^2 = 0.0%		χ^2 = 4.7, df = 1, p = 0.03, I^2 = 78.9%

Abbreviations: P, prospective; R, retrospective.
[*] Original Japanese classification: lower rectum, tumour bulk below or at the peritoneal reflexion (±1 cm); upper rectum, tumour bulk above the peritoneal reflexion.

Table 3
Distal intramural spread below tumour border in patients with pT2 disease treated with surgery without preoperative radiotherapy.

	Design	Total number of patients	Patients with DIS > 0.5 cm below tumour border (%)	Patients with DIS of any length (%)	Maximum length of DIS (cm)	Adjustment for shrinkage[*]
Zhao [15]	P	11	2 (18.2)	2 (18.2)	0.8	Yes
Ono [16]	P	7	1 (14.3)	2 (28.6)	0.6	Yes
Hida [18]	R	38	0 (0)	0 (0)	0	No
Andreola [24]	P	13	1 (7.7)	2 (15.4)	<1.0[#]	No, cork board
Nakagoe [25]	R	21	NG	2 (9.5)	<1.0[#]	No, cork board
Yanagi [26]	P	12	0 (0)	0 (0)	0	No, cork board
Total number		102	8/81 (9.9)	8/102 (7.8)		
Pooled rate (95% confidence interval)			4.7% (1.3–11.5)	9.8% (2.4–21.6)		
Heterogeneity			χ^2 = 8.7, df = 4, p = 0.07, I^2 = 53.9%	χ^2 = 13.7, df = 5, p = 0.02, I^2 = 63.5%		

Abbreviations: DIS, distal intramural spread; NG, not given; P, prospective; R, retrospective.
[#] Precise distance not given.
[*] Adjustment for shrinkage: i.e., "yes" if reported distances were adjusted for tissue shrinkage and the shrinkage ratio was given or "cork board" if the fresh specimen was straightened and pinned on a cork board, which was supposed to give negligible shrinkage [21].

Distal intramural spread

Six relevant references that included 102 patients in total were identified (Table 3, Supplementary Figs. 5, 6) [15,16,18,24–26]. The pooled weighted rate of patients with any DIS was 9.8% (95% CI: 2.4–21.6%) but the heterogeneity was significant in this analysis (p = 0.02). The pooled weighted rate of patients with a spread longer than 0.5 cm was 4.7% (95% CI: 1.3–11.5%). The maximum extent of DIS was 0.8 cm. A large study (n = 150) reported by Shirouzu et al. [27] was not included here because it did not report separate results for pT2. However, it is worth mentioning that no patient with any DIS was reported for pooled pT1 and pT2 tumours.

Lateral lymph nodes

Nine relevant references were identified (Table 4, Supplementary Figs 7, 8) [10,22,28–34]. For a total of 1226 patients with tumour below or at peritoneal reflexion, the pooled weighted rate of patients with LLN metastases was 8.2% (95% CI: 6.7–9.9). For a total of 100 patients with tumour above peritoneal reflection, no patients were recorded with LLN metastases.

Recurrence pattern in patients treated with organ preservation

For watch-and-wait strategy, relevant data were found in ten articles that included 1322 patients in total [35–44]. The pooled rate of the regional nodes recurrences alone (i.e. without concomitant intraluminal recurrences) was 1.0% (95% CI: 0.5–1.7%), $n = 11$, (Supplementary Figs 9, 10A). Precise localization of these recurrent nodes was not given.

For preoperative radiotherapy and local excision, relevant data were found in 25 articles that included 699 patients in total [3,36,39,45–66]. The pooled rate of the regional nodes' recurrences alone was 2.1% (95% CI: 1.2–3.4%), $n = 12$, (Supplementary Figs 9, 10B). Localization of these recurrences was reported only in seven patients [63,65–67]: i.e., perirectal nodes in five cases, internal iliac nodes in one, perirectal and "pelvic wall lymph nodes" in one.

CTV planning study

Based on the above findings, the following rules were proposed for CTV delineation (Table 5): i.e., the caudal border was set 1.5 cm caudally from the tumour to account for DMS or 1 cm caudally from the tumour to account for DIS, whichever is more caudal (see Fig. 1); the S2/S3 interspace was chosen for the cranial border because a great majority of recurrences after radical surgery were located below this level [68–70]; LLNs were included in the CTV up to the S2/S3 interspace in patients with tumour at or below peritoneal reflexion. These rules were used for the $CTV_{proposed}$ delineation. The following rules for $CTV_{standard}$ delineation were used according to the current guidelines [6,7]: i.e., the caudal border was at the pelvic diaphragm or 2 cm caudally from the tumour, whichever is more caudal (see Fig. 1); cranial border at the sacral promontory; and LLNs included into the CTV up to the sacral promontory in all patients.

Table 5
Proposed clinical target volume borders in radiation therapy for organ preservation in patients with cT2 tumour.

Caudal border	1.5 cm caudally from the tumour to account for distal mesorectal spread, or 1 cm caudally from the tumour to account for distal intramural spread, whichever is more caudal (see Fig. 1)
Cranial border	S2/S3 interspace
Lateral border	Pelvic wall for tumours with lower border located below or at the peritoneal reflection to include lateral lymph nodes, or mesorectal fascia for tumours with lower border located above the peritoneal reflection

All eight patients included in our planning study had tumours located below the peritoneal reflection: i.e., mean 4.5 cm (range: 3.5 cm–6.5 cm) from the anal verge. Thus, LLNs were delineated in all patients. The caudal border of the $CTV_{proposed}$ was on average 0.9 cm (range: 0.5 cm–1.5 cm) higher than the corresponding $CTV_{standard}$ border (Fig. 1). The cranial border of the $CTV_{proposed}$ was on average 2.1 cm (range: 1 cm–2.5 cm) lower than the corresponding $CTV_{standard}$ border. The mean $PTV_{proposed}$ was 1152 cm^3 (range: 938 cm^3–1393 cm^3) and the $PTV_{standard}$ was 1401 cm^3 (range: 1169 cm^3–1645 cm^3). The mean relative PTV reduction was 18% (range: 13%–22%). The proposed delineation rules resulted in batter sparing of the anal canal, penis bulb, vagina, small bowel and the bones as well as the reduction of scattered dose to the testicles compared to the standard delineation guidelines (Table 6).

Discussion

Our meta-analysis suggests a 1.5 cm CTV margin caudally from a primary tumour to account for DMS (Table 1) or 1 cm to account for DIS (Table 3), whichever is most inferior (Fig. 1, Table 5); please note that, by definition, DMS is not possible below the lowest level of mesorectum (anorectal junction). Whereas DIS, that extends along the mucosa, might be situated more caudally in tumours located very close to the anorectal junction or invading the anal canal – see Fig. 1B. However, it should be stressed that co-registration of planning CT with MR imaging is needed to adopt

Table 4
Tumour location and the incidence of lateral node metastases in patients with pT2 disease treated with surgery without preoperative radiotherapy.

	Design	Tumours above peritoneal reflexion[#]		Tumours below or at peritoneal reflexion[#]	
		Total number of patients	Number of patients with lateral node metastases (%)	Total number of patients	Number of patients with lateral node metastases (%)
Tan [28]	R	NG	NG	301	16 (5.3)
Hojo [22]	R	20	0 (0)	62	4 (6.5)
Hida [29]	R	18	0 (0)	20	0 (0)
Ueno [30]	R	NG	NG	6	1 (16.7)
Funahashi [31]	R	NG	NG	11	1 (9.0)
Kanemitsu [32]*	R	NG	NG	348	35 (10.1)
Kobayashi [33]	R	NG	NG	207	17 (8.2)
Watanabe [10]^	R	18	0 (0)	218	20 (9.2)
Koda [34]*	R	44	0 (0)	53	5 (9.4)
Total		100	0 (0)	1226	99 (8.1)
Pooled rate (95% confidence interval)			0.9% (0.0–5.2)		8.2% (6.7–9.9)
Heterogeneity			$\chi^2 = 0.2$, df = 3, $p = 1.0$, $I^2 = 0.0\%$		$\chi^2 = 9.9$, df = 8, $p = 0.3$, $I^2 = 18.9\%$

Abbreviations: NG, not given; P, prospective; R, retrospective.
^ We cannot be sure that the patients data presented in the report by Watanabe et al. [10], which was based on the multi-institutional registry, does not overlap in part with the patient data reported by other Japanese authors.
# Original Japanese classification: lower rectum, tumour bulk below or at the peritoneal reflexion (±1 cm); upper rectum, tumour bulk above the peritoneal reflexion.
* A minority of patients received preoperative radiation (the exact number of patients with preoperative radiation was not specified).

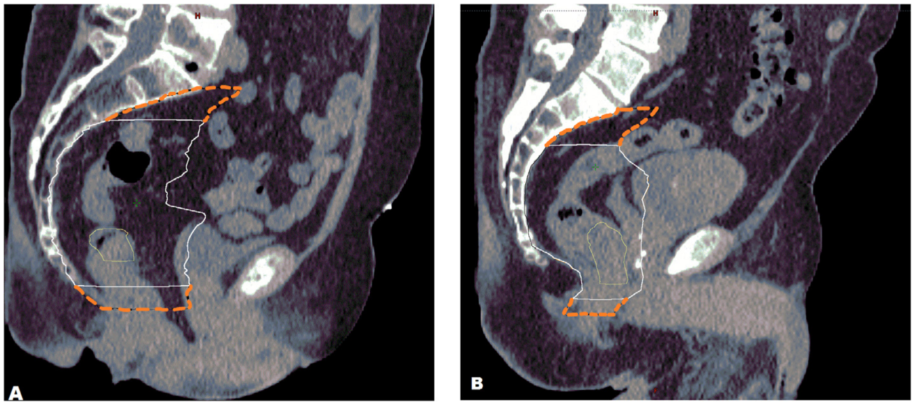

Fig. 1. Comparison of clinical target volume (CTV) obtained after applying the proposed rules to that obtained after using the current guidelines. Solid line - $CTV_{proposed}$; dashed line – $CTV_{standard}$; thin line – gross tumour. (A) cT2 cancer situated 6 cm from the anal verge in a 70-year-old woman treated with organ-preserving intent. Excision of the uterus had been performed previously. The $CTV_{proposed}$ caudal border was set at 1.5 cm from the tumour to account for distal mesorectal (DMS) and intramural spread (DIS). The respective $CTV_{standard}$ border was located at the pelvic diaphragm. Note that after addition of a 1 cm margin for planning target volume (PTV), the whole anal canal (V_{50}: 0 cm^3 vs 5 cm^3) and larger part of the vagina (V_{50}: 1.6 cm^3 vs 5 cm^3) were spared when $CTV_{proposed}$ was used compared with $CTV_{standard}$. This may result in better anorectal functioning [82]. Lowering the upper $CTV_{proposed}$ border to the S2/S3 interspace resulted in better small bowel (V_{45}: 118 cm^3 vs 132 cm^3) and bone sparing. Thus, better gastrointestinal and haematological tolerance [78,79] as well as lower risk of insufficiency fractures [87] are expected. (B) cT2 cancer situated 3 cm from the anal verge in a 61-year-old man treated with organ-preserving intent. The tumour abuts the upper edge of the anal canal. The $CTV_{proposed}$ caudal border was set at 1 cm from the tumour to account for DIS. The respective $CTV_{standard}$ border was located 2 cm from the tumour [7]. After addition of a 1 cm margin for PTV, a larger volume of the anal canal was spared (V_{50}: 14 cm^3 vs 23 cm^3). This may result in better anorectal function when an organ-preserving strategy is used [82] or in lower risk of perineal wound healing delay in the event of abdomino-perineal resection [89]. In addition, applying $CTV_{proposed}$ resulted in better sparing of the penis bulb (D_{70}: 40 Gy vs 43 Gy) and lower scattered dose to the testicles (mean dose for both testicles: 0.7 Gy vs 0.9 Gy).

Table 6
Dose–volume parameters for organs-at-risk in eight patients with cT2 tumour in relation to the rules used for CTV delineations.

	Proposed delineation Mean (range)	Standard delineation Mean (range)	Mean relative reduction (range)
V_{45} of the small bowel [cm^3]	41.9 (0.0–117.9)	88.6 (8.2–180.0)	69% (11%–100%)
V_{50} of the anal canal [cm^3]	5.5 (0.0–13.9)	9.4 (1.7–22.6)	46% (6–100%)
Mean dose in the testicles [Gy] ($n = 7$)	0.9 (0.3–1.7)	1.1 (0.4–2.3)	19% (6–26%)
Dose in the penis bulb D_{70} [Gy] ($n = 7$)	12.6 (4.2–39.6)	20.1 (5.2–42.9)	31% (8–79%)
V_{50} of the vagina [cm^3] ($n = 1$)	1.6	5.8	72%

the above rules. Otherwise, CT image resolution is often insufficient to determine the tumour's border.

The necessity of inclusion of LLN in the CTV for early rectal cancer has been questioned [8,9]. However, surprisingly, our review showed that for low-lying pT2 tumours, the pooled rate of patients with metastases to these nodes was as high as 8.2% (Table 4) and occasionally nodal recurrences were reported in this region in patients treated with organ preservation. In addition, the importance of elective treatment of LLN was shown by the recent Japanese randomized study [71]. In this trial, 701 patients with clinical stage II/III low-lying cancer were treated with either TME alone or TME combined with LLN dissection. The rates of patients with local recurrences were 13% vs. 7%, $p = 0.024$ and the rates of those with lateral recurrences 7% vs. 2%, respectively, $p < 0.05$. Moreover, in the Western countries LLN are not resected at TME. For these reasons, we have decided in our planning study to include LLN in the $CTV_{proposed}$ for tumours at or below peritoneal reflexion. However, our decision remains controversial because there are other evidences showing that the risk of recurrence in the lateral compartment is very low. For example, the Swedish study demonstrated that only two recurrent tumours appeared to originate from the lateral pelvic lymph nodes among 880 patients of whom 60% received preoperative radiotherapy and 40% TME alone [72]. Moreover, one may expect that the risk of late complications increases with inclusion of the LLN into CTV. Therefore, we performed an unplanned comparison of the treatment plans with and without inclusion of LLN into $CTV_{proposed}$ in the first three patients from our planning study group. Although exclusion of LLN from the CTV resulted in the mean PTV reduction of 300 cm^3, additional sparing of the organs-at-risk was small; the mean reduction of the small bowel V_{45} was 9 cm^3, the anal canal V_{50} 0.3 cm^3, the mean dose in the testicles 0.3 Gy and the penis bulb D_{70} 0.2 Gy. It should, however, be noted that the risk of venous thromboembolism might decrease with exclusion of the internal iliac vessels and their branches from CTV [73].

The rate of upward lymphatic spread (along the superior rectal and inferior mesenteric artery up to its root, with an approximate landmark between the S2/S3 interspace and L3) for pT2 cancers was meaningful even in low-lying tumours (6.0%) (Table 2). Thus, the question arises whether CTV must include the upward spread to treat all at-risk nodes given that they are untouched by surgery if organ-preserving treatment is used. Several issues must be considered in answering this question. Firstly, we have not found in the literature any patient with relapse in nodes above the sacral promontory (cranial CTV borders) after organ preservation. Secondly, the global watch-and-wait strategy implies rectal preservation only in radiosensitive cancers and radical surgery for radioresistant tumours that persist after radiotherapy. Similarly, the preoperative radiotherapy and local excision strategy implies rectal preservation only in radiosensitive cancers (i.e., in those downstaged to ypT0-1 disease) and conversion to radical surgery when the pathological report of a local excision specimen shows poor tumour response [5]. In this context, it is worth observing that high tumour radiosensitivity is associated with low cancer aggressiveness [38,74,75] (i.e., with low propensity for distant and local recurrences). Therefore, it might be expected that nodal disease is cranially situated not far away from a primary tumour in inherently radiosensitive cancers [76]. In contrast, high cancer aggressiveness is associated with upward lymphatic spread [22,77]. Therefore, it might be expected that the risk of upward spread in radioresistant cancers is clinically meaningful. However, the tissue harbouring this spread is removed during the radical surgery needed in such cases. Thirdly, in patients with advanced cancer after radical surgery without preoperative radiotherapy, a great majority of local recurrences were located below the S2/S3 interspace [68–70]. Taken together, the S2/S3 interspace might be chosen as a cranial CTV border in patients undergoing organ-preserving strategy for cT2 cancer.

We proposed new delineation rules based on the evidence (Table 5). Compared to the delineations performed according to the published guidelines [6,7], we showed an 18% relative reduction of PTV on average. Consequently, dose–volume parameters favour the proposed rules for the following organs-at-risk: small bowel, anal canal, testicles and penis bulb, pelvic bones and vagina (Table 6, Fig. 1). These may result in lower risk of acute gastrointestinal [78] and haematological [79] toxicity as well as late toxicity: e.g., anorectal dysfunctions [80–82], sexual dysfunction [83,84], male hypogonadism [85,86], insufficiency fractures [87], small bowel obstruction [88] and perineal wound healing delay [89]. Two aspects are worth emphasizing in the context of only minor reduction of lower CTV border (mean 0.9 cm). Firstly, radiotherapy used for organ preservation causes anorectal dysfunctions that are similar to anterior resection syndrome [80,81]. Because faecal incontinence is strongly related to the volume of irradiated sphincters [82], improvement of anorectal functioning is expected by applying the proposed rules. Notably, we demonstrated a 46% relative reduction of the irradiated anal canal volume using these rules (Table 6). Secondly, hypogonadism resulting from a small scattered dose in the testicles is strongly related to the location of the lower CTV border [85,86]. We also demonstrated a 19% relative reduction of the mean testicles dose using the proposed CTV delineation rules (Table 6).

Our study has several limitations. Some of the included articles have a low level of scientific evidence and this has an impact on the strength of the final results. We included only reports showing results in pT2 disease. However, decisions about radiotherapy for organ preservation are based on clinical staging, which may erroneously diagnose some pT3 lesions as cT2. The data on cancer spread mostly came from Japan. It is not clear whether the tumour biology is similar between Western and Japanese populations. Bias might be present in the evaluation of the rate of involvement of LLN because the Japanese guidelines recommend LLN dissection in all patients with II–III clinically staged tumours and as an option for cT2N0 cancers. Therefore, dissection of these nodes might be performed only for patients with advanced cT2 lesions; e.g., when enlarged nodes are found at surgery or when cT3 disease turns out to be pT2. Thus, it is likely that the incidence of LLN metastases is overestimated by our meta-analysis. However, the incidence of positive LLN was 7.5% (13/173) in institution where LLN dissection was performed routinely for all low cT2 tumours [32], which is not meaningfully different from the 8.2% pooled rate calculated by this meta-analysis. Some reports included in our review may underestimate the extent of cancer spread because they evaluated only nodal involvement without examining extranodal cancer deposits (Table 1). Moreover, no correction for tissue shrinkage after fixation was applied in some studies and only a few reported using a fat clearing method (Tables 1–3). Low total number of patients included in the analysis is another limitation of our study, suggesting caution in the interpretation of the results.

In conclusion, our meta-analysis suggests a smaller CTV for patients with cT2 tumour to that recommended by the current guidelines designed for advanced cancers.

Conflicts of interest

No potential conflict of interest to disclose

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.12.024.

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