

Reduced pelvic field sparing anastomosis for postoperative radiotherapy in selected patients with mid–upper rectal cancer

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ABSTRACT

The aim of this study was to report the clinical results of reduced pelvic field radiotherapy (RT), excluding the anastomotic site, after total mesorectal excision in selected patients with rectal cancer. Between 2011 and 2014, 99 patients underwent upfront surgery for clinically less-advanced tumors but were finally diagnosed as pT3/N+. Among them, 50 patients with mid–upper rectal cancer who received postoperative RT with a reduced pelvic field were included in this retrospective review. This group was composed of patients with high seated tumors, complete resection with a clear circumferential resection margin, and no complication during surgery. We investigated treatment outcomes, toxicity and the effect of RT-field reduction on organs-at risk in 5 randomly selected patients. During the median follow-up period of 42 months (range: 15–59 months), tumors recurred in 9 patients (18%). The 3-year overall and disease-free survival were 98% and 81%, respectively. Distant metastasis was the dominant failure pattern ($n = 8$, 16%), while no recurrences occurred at or near anastomotic sites. No anastomotic complications were found on pelvic examination, images and/or colonoscopy. Reported acute and late RT-related toxicities were mostly mild to moderate, with only small numbers of Grade 3 toxicities. None of the patients developed Grade 4–5 acute or late toxicity. With a caudally reduced field, 64% reduction in absolute anastomotic exposure at the maximum dose was achieved compared with the traditional whole-pelvic field ($P = 0.008$). The reduced pelvic field RT was able to minimize late anastomotic complication without increasing its recurrence in selected patients with mid–upper rectal cancer in the postoperative setting.

KEYWORDS: anastomosis, local recurrence, postoperative, rectal cancer, whole-pelvis radiotherapy

INTRODUCTION

In recent years, improvements in diagnosis, staging, and multimodal treatments have provided both local control and survival benefits to patients with rectal cancer [1, 2]. There is considerable evidence that for many patients with locally advanced rectal cancer, pelvic radiotherapy (RT), in addition to total mesorectal excision (TME), results in improved local control and increased probability of

sphincter preservation in low-seated tumors [3, 4]. Although preoperative RT is the standard of treatment for locally advanced tumors [5, 6], a substantial number of patients still require postoperative chemoradiotherapy (CRT) for unfavorable pathologic features after upfront surgery for less-advanced tumors. Nevertheless, there is also substantial evidence that the use of pelvic RT may be associated with early and late adverse effects, such as wound

complications, impaired anal function and fecal incontinence, increased risk of late bowel obstruction, and even more serious consequences, such as secondary malignancies [7–9]. It therefore appears that balancing the potential survival benefit and the toxicity risk is important when planning RT, in order to adapt the dose distribution to targets so as to avoid normal tissue, thereby maximizing the therapeutic ratio.

Multiple factors, including surgical modality, circumferential resection margin (CRM) status, risk classification group based on Gunderson's pooled analysis [10], distance from the anal verge, total nodal count (as a surrogate of surgical quality), and perforation in the tumor area, has an impact on the risk of local recurrence (LR) and patterns of failures. A comparison of failure patterns has suggested that the presacral space is the dominant site of local recurrence after surgery + RT or CRT in the TME era [3]. The anastomosis, which is one of the common involvement sites, is associated with residual mesorectal fat after incomplete surgery. High-seated tumors are associated with low rates of LR, since it is possible to achieve a clear resection margin at the rectum above the peritoneal reflection, and surgery in this region is technically less demanding [3, 11, 12]. In addition, lymphatic spread occurs mainly in the upward direction, along the inferior mesenteric nodes, in high-seated tumors [13]. Taken together, at our institution, a multidisciplinary consensus was reached in 2011 to implement a caudally reduced radiation field excluding the anastomotic site, for selected patients in the post-operative clinical setting. To implement this approach, the tumors should be high-seated, with a relatively low risk of LR (complete TME, adequate CRM, and without perforation of or leakage from the anastomotic site during surgery).

In this study, we investigated the clinical outcomes of RT using a reduced field in locally advanced rectal cancer with a mid–upper location, by reviewing the patterns of failure, efficacy, and toxicity, and attempted to determine whether this reduced field RT could be performed safely in carefully selected patients. In addition, the potential benefit in terms of the irradiated dose at the anastomotic site was determined by dosimetric comparison for use of the conventional three-field whole-pelvic field with use of the reduced pelvic field.

MATERIALS AND METHODS

Patients

The schematic flow of patient selection is shown in Fig. 1. In brief, postoperative CRT was recommended for all TME patients who received no preoperative treatment with a CRM involvement, had perforation in the tumor area, and/or with a diagnosis of \geq pT3 or pN+ rectal cancer. A total of 99 patients with pT3 or pN+ (no T4) rectal cancer received TME from March 2011 to September 2014 at our institution. (i) Traditional pelvic field radiation was used in cases of R1/2 resection ($n = 15$), low-seated tumors ($n = 13$), surgical complications ($n = 13$), and technical issues that limited the use of a reduced pelvic field ($n = 7$). (ii) The remaining 51 patients who underwent complete TME, with a clear CRM, for high-seated tumors, and who were without surgical complications and technical limitations, received reduced-field RT. After excluding 1 patient who could not receive the full course of RT, 50 patients were

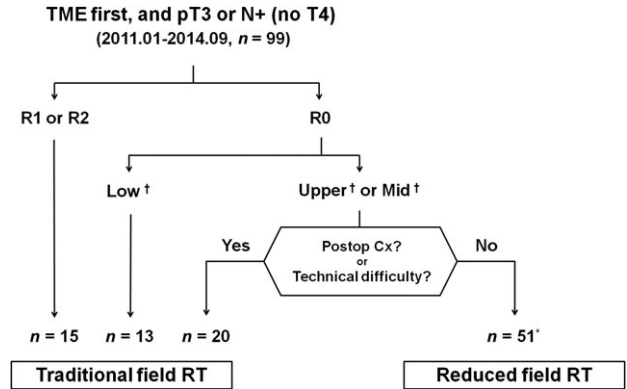


Fig. 1. Flow chart of patients with rectal cancer who were treated with upfront TME \pm postoperative RT in our institution (January 2011 – September 2014). Asterisk indicates postoperative RT in reduced pelvic field ($n = 51$); of the 51 patients, 50 patients were included in our analysis. Dagger indicates the height of the tumor is classified as upper, mid, or low, according to the location of the tumor on T2-weighted sagittal MRI scans, as described in a previous report [14].

included in this analysis. In addition, 491 patients received preoperative CRT during the same period. The level of the tumor was classified according to the peritoneal reflection, using T2-weighted sagittal images obtained by magnetic resonance imaging (MRI), as being high- (upper) or low-seated (lower-middle) tumors, as described in a previous report [14]. Low- or mid-rectal cancers were divided using a virtual line, which was defined as the line from the symphysis pubis to the levator muscle origin on the sacrum on the sagittal T2-weighted images. The details of data collection are described in Supplementary Text 1. This study was approved by the institutional review board (IRB) of the Yonsei University Health System. The patient records/information was anonymized and de-identified prior to this retrospective analysis, so informed consent was not obtained from each participant.

Radiotherapy

Postoperative RT was delivered in a reduced pelvic field with a radiation dose of 45 Gy, divided into 25 fractions, in a single phase, using 3D conformal RT. Contrast-enhanced computed tomography (CT), with slices of 5-mm-thickness, was performed to plan the RT; the patient was instructed to maintain a full bladder in the prone position using a belly board with bladder compression device during the planning CT scan. Protocol-based full-bladder maintenance (which consisted of education, training and continuous bio-feedback by measuring bladder volume) was performed throughout the treatment sessions [15, 16]. The CT scan was imported to the Pinnacle planning system version 9.4 (Philips Medical Systems, Cleveland, OH) and MIM software version 6.0.6 (MIM Software Inc., Cleveland, OH), and the clinical target volume (CTV) was delineated on each of the axial CT images by an experienced radiation oncologist.

The CTV was not a classic pelvic volume, but was a caudally reduced pelvic field that omitted the anastomotic site. The CTV comprised the presacral, perirectal, internal iliac, and obturator lymph node areas. Its outline was made 1–1.5 cm above the level of the anastomotic site, with an intention to avoid irradiation of this site. The CTV included parts of the bladder anteriorly and parts of the sacrum posteriorly, considering possible motion in that area during the treatment. A 3–5 mm set-up uncertainty margin was applied to the CTV to create the planning target volume (PTV). The upper limit of the reduced pelvic irradiation field was S1, and the lower limit was 1 cm below the PTV. A 6-MV posterior photon beam and 10-MV lateral opposing photon beams were used for the reduced pelvic field (Fig. 2). All fields were treated daily. Port films were obtained weekly, or more often if clinically indicated.

Plan comparison

We performed a dosimetric comparison between the reduced-field and traditional three-field whole-pelvic field in five randomly

selected patients. An additional RT plan was generated in the traditional whole-pelvic field (45 Gy, in 25 fractions) for each patient, and D_{max} , D_{mean} , V_{30} and V_{40} of each organ at risk (OAR) were compared. OARs included the small bowel, bladder, anus, and bilateral femur heads. We contoured the ‘anastomosis’ OAR, including the rectum and perirectal tissue, on each slice demonstrating the anastomosis, to compare the irradiated dose at the anastomosis.

Toxicity and treatment outcome

Patients were seen by a clinician at least weekly during RT and at 1 month after completion of RT, to assess toxicity and to perform a complete blood count (CBC) test. Toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE v. 4.0). Acute toxicity was defined as any event occurring during RT or within 3 months of treatment completion, and late toxicity was defined as events occurring later than 3 months after the end of treatment.

Patients were evaluated at 3-month intervals for the first year, 6-month intervals for the next 2 years, and 12-month intervals

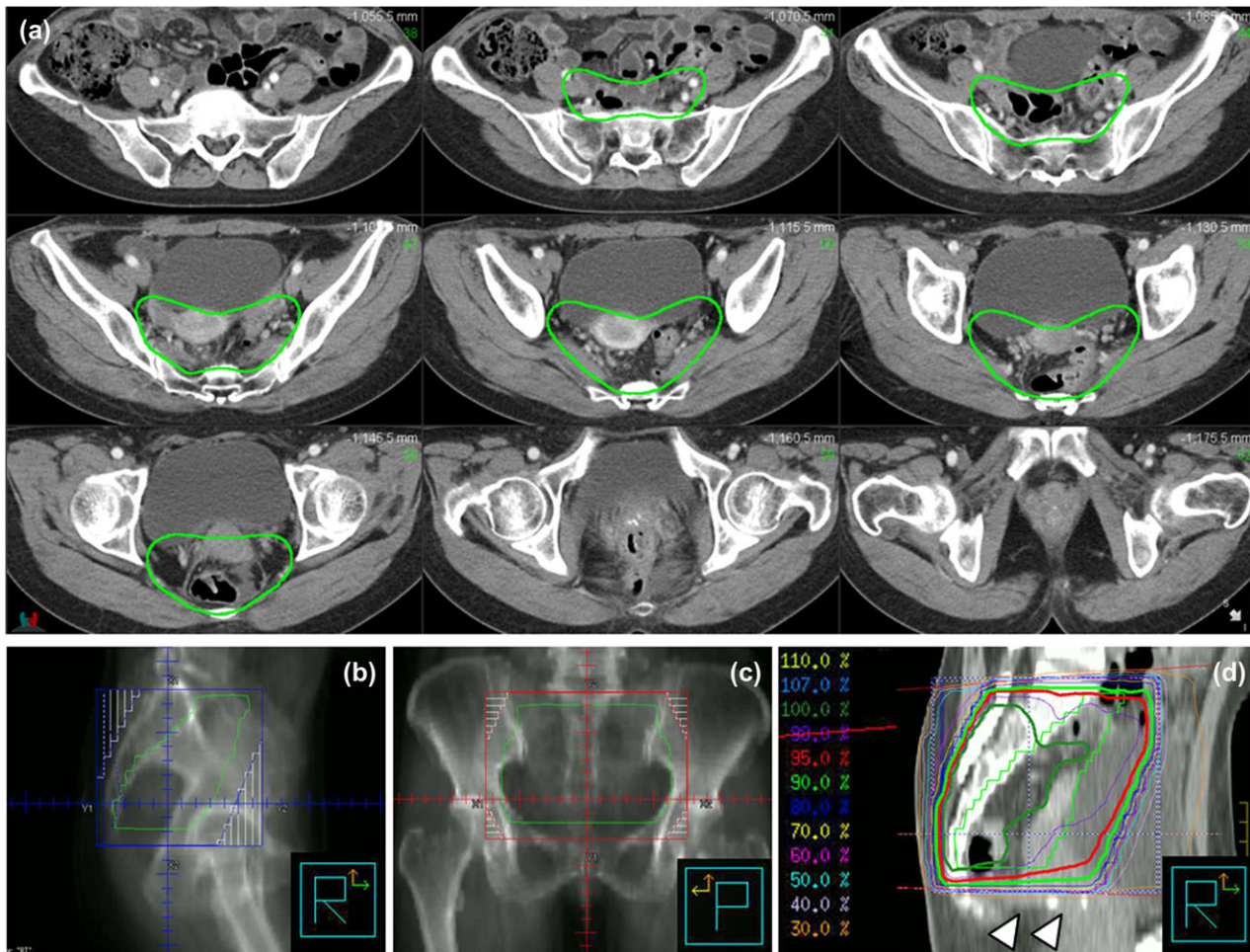


Fig. 2. Example of reduced pelvic field. (a) An example of PTV delineation on each slice of the planning CT scan. The beam's eye views of the right lateral field (b) and postero–anterior field (c). (d) An isodose curve of the reduced pelvic field. The anastomotic site (white arrowhead) is not included in the irradiation field.

Table 1. Patients' characteristics

Variables	No.	%
Age (year)	Median 62 (34–81)	
Sex		
Male	35	70
Female	15	30
Tumor location		
Upper	21	42
Mid	29	58
Clinical AJCC stage		
cT1N0	1	2
cT1/2N0	6	12
cT1/2N1	1	2
cT2N0	3	6
cT2/early cT3N0	2	4
cT2/early cT3N1	3	6
Early cT3N0	21	42
Early cT3N1	11	22
Advanced cT3N2	1	2
Unknown	1	2
Pathologic AJCC stage		
pT1N1	3	6
pT2N1	15	30
pT3N0	11	22
pT3N1	16	32
pT3N2	5	10
PNE		
Positive	6	12
Negative	44	88
LVI		
Positive	12	24
Negative	38	76
PNI		
Positive	6	12
Negative	44	88

Table 1. Continued

Variables	No.	%
Proximal margin (cm)	Median 8.9 (1.0–17.0)	
Distal margin (cm)	Median 2.3 (1.0–27.0)	
Circumferential margin (cm)	Median 1.0 (0.3–2.2)	

AJCC = American Joint Committee on Cancer; PNE = perinodal extension; LVI = lymphovascular invasion; PNI = perineural invasion. Clinical T3 stage rectal cancers are classified as more advanced stage T3 tumors ('Advanced cT3', >5 mm invasion outside the muscularis propria) or early stage T3 tumors ('Early cT3', ≤5 mm invasion outside the muscularis propria) using preoperative MRIs.

thereafter. Routine follow-ups included colonoscopy, serum carcinoembryonic antigen (CEA) tests, abdominal CT and/or pelvic MRI, and toxicity evaluation. When recurrence was suspected, further assessments were performed by colonoscopy with histological confirmation and imaging studies, including MRI. LR was defined as any recurrence inside the pelvis, with or without extrapelvic recurrences. All other recurrences were defined as distant metastases (DMs).

Statistical analysis

SPSS ver. 20 (IBM, Armonk, NY, USA) was used for statistical analyses. Recurrence-free survival (RFS), local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS) and overall survival (OS) rates were defined as the time from the date of surgery to any recurrence or last follow-up, to local recurrence or last follow-up, to distant metastasis or last follow-up, and to death from any cause or last follow-up, respectively. These rates were calculated using the Kaplan–Meier method, and prognostic impacts of clinical factors were analyzed with the log-rank test. Cox regression was used for identification of independent prognostic factors by multivariate analysis. *P*-values <0.05 were considered statistically significant.

RESULTS

Clinical and pathological characteristics

In this group of patients, 42% of tumors were located in the upper-third and 58% were located in the mid-third of the rectum. In terms of the initial clinical American Joint Committee on Cancer (AJCC) stage, all except for 1 patient, who could not receive preoperative CRT due to urgent cardiac problems, were diagnosed as having cT1/2 (*n* = 11, 22%) or early cT3 stage (*n* = 37, 74%) tumors. Sixteen patients (32%) were diagnosed with clinical N+ stage. Forty-nine patients (98%) underwent low anterior resection (LAR), and all patients received complete resection (R0).

In the final pathological AJCC stage, all patients had pT3 (*n* = 32, 64%) or pN+ (*n* = 39, 78%) stage tumors, and 29 patients (58%) were classified as belonging to the intermediate-risk group (pT1N1, pT2N1, pT3N0). Patient and tumor characteristics are summarized in Table 1. Details of chemotherapy regimens are shown in Supplementary Text 2.

Continued

Patterns of recurrence

During the median follow-up period of 42 months (range: 15–59 months), tumors recurred in 9 patients (18%). DM was the dominant failure pattern ($n = 8$, 16%), while LR occurred in only 1 patient (2%), at 9 months postoperatively (Supplementary Table 1). The majority of recurrences were discovered in patients with pT3 stage tumors (DM 7, LR 1). In the latter patient with LR, the recurring tumor was located in the presacral area, which was included in the irradiated area and was associated with multiple adverse pathological features (poorly differentiated adenocarcinoma, with signet ring cell features, multiple regional LNs (10/27), lymphovascular invasion (LVI) and perineural invasion (PNI). In the 8 patients with DM, the metastases occurred mostly within 1 year (median: 9.5 months) after surgery. DMs were most commonly observed in the lung ($n = 4$), while others were observed in the liver ($n = 1$), liver and lung ($n = 1$), liver and portocaval/hepato-duodenal lymph nodes ($n = 1$), or peritoneum ($n = 1$).

Toxicity

There were no anastomotic complications after surgery, based on pelvic examination, imaging, and/or colonoscopy, up to the last follow-up date. Reported acute and late RT-related toxicities were mostly mild to moderate, with only small numbers of Grade 3 toxicities. Acute toxicities included fatigue, anorexia, nausea, cystitis, diarrhea, anal incontinence, or skin rash, and late toxicities included

diarrhea or anal incontinence (Table 2). The only Grade 3 toxicity observed was diarrhea [acute: 15 (30%), late: 13 (28%)]. None of the patients developed Grade 4–5 acute or late toxicity.

Survival and prognostic factors

The RFS, LRFS, DMFS and OS rates at 3-year follow-up were 81%, 98%, 83% and 98%, respectively (Fig. 3). Only the survival rates for patients with T3 stage tumors were slightly worse (75%, 96%, 78% and 95%, respectively). At the last follow-up, only 1 disease-related death had occurred, at 27 months after surgery, after DM involving both the liver and the lung. Clinical features were then evaluated to determine their prognostic significance for RFS, and the following factors were found to be related to worse RFS in univariate analysis: N2 stage, Stage IIIC, LVI and PNI (all $P_s < 0.05$). Among these factors, LVI was the only significant factor in multivariate analysis ($P = 0.039$) (Supplementary Table 2).

Dosimetric comparison

Compared with the traditional whole-pelvic field RT, a significantly lower dose was delivered to the anus and anastomosis by using the reduced pelvic field. Although the dose varied according to the height of the pelvis and the anastomosis, D_{max} was reduced by an average of 6% and 36% at the anus and anastomotic site, respectively. The average values of D_{max} , D_{mean} , V_{30} and V_{40} of other OARs were all similar (Table 3).

Table 2. Incidence of acute and late toxicity after radiotherapy

Grade	Acute toxicity [No. (%)]						Late toxicity [No. (%)] ^a		
	Fatigue	Anorexia	Nausea	Cystitis	Diarrhea	Anal incontinence	Skin rash	Diarrhea	Anal incontinence
0	8 (16)	11 (22)	45 (90)	43 (86)	20 (40)	41 (82)	48 (96)	10 (21)	43 (92)
1	35 (70)	33 (66)	4 (8)	6 (12)	4 (8)	8 (16)	0 (0)	8 (17)	4 (8)
2	7 (14)	6 (12)	1 (2)	1 (2)	11 (22)	1 (2)	2 (4)	16 (34)	0 (0)
3	0 (0)	0 (0)	0 (0)	0 (0)	15 (30)	0 (0)	0 (0)	13 (28)	0 (0)

^aThree patients with unknown late toxicity information were excluded.

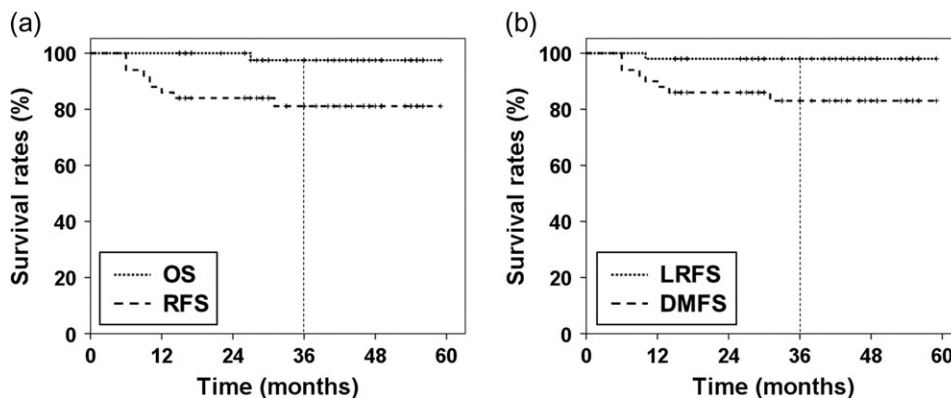


Fig. 3. Survival curves: (a) overall survival (OS) and recurrence-free survival (RFS), and (b) local recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) rates in 50 patients.

Table 3. Irradiated dose and volume for OARs in conventional whole-pelvis and reduced pelvic field

OAR	Whole pelvis	Reduced pelvis	P value ^a
Small bowel			
D _{max} (Gy)	29.82	29.96	0.917
V ₃₀ (%)	11.94	11.48	0.841
V ₄₀ (%)	9.92	9.46	0.841
D _{mean} (Gy)	9.83	9.57	0.690
Bladder			
D _{max} (Gy)	46.23	45.44	0.056
V ₃₀ (%)	51.54	41.23	0.421
V ₄₀ (%)	45.18	33.93	0.222
D _{mean} (Gy)	29.04	25.11	0.310
Anus			
D _{max} (Gy)	46.36	2.60	0.008
V ₃₀ (%)	79.05	0.00	0.008
V ₄₀ (%)	74.43	0.00	0.008
D _{mean} (Gy)	37.19	1.67	0.008
Anastomosis^b			
D _{max} (Gy)	46.95	16.88	0.008
V ₃₀ (%)	100.00	2.76	0.008
V ₄₀ (%)	100.00	0.43	0.008
D _{mean} (Gy)	45.56	6.12	0.008
Rt. femur head			
D _{max} (Gy)	43.19	37.45	0.222
V ₃₀ (%)	58.89	16.26	0.056
V ₄₀ (%)	2.62	0.96	0.421
D _{mean} (Gy)	25.51	12.79	0.056
Lt. femur head			
D _{max} (Gy)	43.49	35.76	0.421
V ₃₀ (%)	50.76	15.89	0.032
V ₄₀ (%)	2.70	1.11	0.310
D _{mean} (Gy)	23.71	11.93	0.056

OAR = organ-at-risk.

^aAnastomosis OAR was contoured, including rectum and perirectal tissue in each slice showing anastomosis.^bThe Mann-Whitney U-test was used.

DISCUSSION

This study investigated the possibility that using a reduced pelvic field RT, which spared the anastomotic site, could minimize late anastomotic complications, without increasing tumor recurrence in selected rectal cancer patients in the postoperative setting. The selection process included a consideration of (i) the completeness of TME with a clear CRM, (ii) the location of the tumor (mid/upper tumors were selected) and (iii) the complete absence of postoperative complications. We observed a non-increased risk of recurrence or late complications at the anastomotic site, up to the median follow-up period of 42 months. Thus, our study suggests that reduced-field RT can be used postoperatively with success in carefully selected patients.

Since the introduction of TME, local failure has decreased dramatically, with further improvement in treatment success brought about by addition of pelvic RT. In a Dutch trial with a median follow-up of 12 years, the 10-year LR rates were 5% in the RT + TME group and 11% in the TME-only group [4]. It has also been reported that there are many pathological or therapeutic factors that affect the risk of LR in the TME era. First, one of the major prognostic factors of LR after resection is a positive CRM and/or distal resection margin, with the probability of residual tumors. CRM involvement was found to be a risk factor for LR as well as DM in several studies, including the Dutch TME trial, which reported a 17% LR rate in patients in whom the CRM was involved [3, 17, 18]. A study from the Memorial Sloan-Kettering Cancer Center found that residual tumors were observed more frequently when the tumor was distally located [19]. It has generally been recommended that a distal margin of 1–2 cm be used in TME to assure removal of all local diseased tissue. Even a distal margin of 1 cm was considered sufficient to eliminate all occult tumor extensions beneath the gross mucosal edge in patients receiving pelvic RT plus TME [19]. Second, the location of the tumor within the rectum is also a critical factor, as high-seated tumors are covered by the peritoneum and a clear margin is more easily achievable with TME. The LR rate was reported as 10–15% for tumors located in the lower third, which was higher than for tumors located in either the middle third (5–10%) or upper third (2–5%) [11, 12]. Therefore, it is plausible that mid-upper rectal cancers with a sufficient clear surgical margin would have a relatively low risk for LR.

Some knowledge of the anatomic pattern of LRs after rectal cancer surgery would aid in defining the optimal RT target volume. Earlier studies [20] assessed the predominant location of LRs, and defined the guidelines for delineation of a CTV that includes the primary tumor, the mesorectal subsite, the posterior pelvic subsite, and the lateral lymph nodes. Although limited data are available on failure patterns in the TME era, LR remains the predominant pattern of failure, and presacral recurrences were the most common type of LR (25% with TME alone, and 15% with TME + RT, according to the Dutch TME trial) [3]. Presacral recurrences had a generally poor prognosis, with an OS rate of 22.5%. Anastomotic recurrences were less common (9% with TME alone, 5% with TME + RT) and had a relatively good prognosis. Anastomotic recurrence has traditionally been attributed to inadequate resection margins or implantation of exfoliated cancer cells when creating the anastomosis. Syk *et al.* reported that high-seated tumors showed

LRs mainly in the anastomotic site, and most of these (12/14) were accompanied by evidence of residual mesorectal fat [21]. In other words, LR seldom recurred at the anastomotic site when no residual tumors were left after surgery.

Anastomotic leakage (AL), one of the most detrimental complications after TME, could be associated with long-term oncological outcomes, and with LR in particular. A recent systemic review [22] has reported that the LR rate increased after AL in patients undergoing resection for colorectal cancer (odds ratios: 2.05, 95% CI: 1.51–2.8, $P = 0.0001$). Although the mechanism by which AL may enhance tumor recurrence remains uncertain, several studies suggested that AL could lead to extra-luminal implantation of exfoliated cancer cells from the bowel lumen or to local inflammatory responses. Taken together, it can be inferred that TME with a clear CRM, and high-seated tumors resected without surgical complications result in a low risk of recurrence at the anastomotic site, and that LR will most frequently occur in the presacral area. Our findings of a low LR rate (2%, no outfield LR) and high DM rate as a predominant pattern of failure (16%) support this hypothesis.

Although RT delivers tumoricidal doses of radiation to the microscopic tumor cells in the pelvic cavity, the normal tissue in the irradiated field is also subject to injury. In a postoperative RT trial, 13 patients (6.7%) overall had severe delayed reactions, including small bowel obstruction, hemorrhage, enterocutaneous fistula, and rectal perforation [23]. Fractionated doses of RT induce a 15% increase in the incidence of severe late complications in the small bowel [24]. Hassan *et al.* demonstrated that patients receiving pelvic RT had a higher rate of anastomotic complications, other than strictures, including fecal incontinence, fistulas, abscesses, and bowel obstructions, than patients not receiving pelvic RT (5-year: 20% vs 5%, $P = 0.0001$) [25]. Although there have been some efforts to reduce radiation doses to the small bowel in pelvic RT for rectal cancers in recent years [21, 26–28], the effect of omitting the anastomotic site in postoperative RT has not been investigated previously. It is plausible that a reduced dose and volume of radiation to the anastomotic site will lead to reduced late toxicity without compromising local tumor control.

The effect on anal and anastomotic site exposure achieved by using a reduced pelvic field is shown in Table 3; an average 94% and 64% reduction in D_{\max} was shown, respectively, as compared with the typical three-field whole-pelvic treatment approach. This is likely to yield a significant reduction in both acute and late bowel and anastomotic toxicity. It should also be noted that, even up to the last follow-up evaluation in our study, no acute or late toxicity related to the anus or anastomotic site were observed. However, further prospective studies with a longer follow-up duration are needed to confirm this observation, particularly in terms of late toxicity.

This study had some limitations. First, our study included a small number of patients due to the low referral rates for postoperative RT. Second, there is a possible patient selection bias due to the retrospective study design. Because the majority of tumors with high-risk features first receive preoperative RT, tumors with a relatively low risk of LR would be referred for postoperative RT. However, even in patients with pN+ stage, perinodal extension, LVI, or PNI, no LR occurred outside the smaller irradiated volume used for RT in our study. A third limitation was the relatively short

follow-up duration, of a median of 42 months. However, this period is quite adequate for considering the early outcome of postoperative RT; it compares well with previous studies in the TME era that reported a median of 17–30 months to LR [9, 27, 29]. Moreover, the postoperative CRT group tended to develop early LR (<5 years) more often than the group receiving preoperative CRT, despite the chance of late recurrences [30].

CONCLUSION

In conclusion, the use of a reduced pelvic field, omitting the anastomotic site, for RT is a feasible postoperative treatment option for clearly resected rectal cancers with a mid–upper location; this could increase the safety of postoperative RT. Further studies with a longer follow-up duration, larger patient cohort, or a prospective setting are warranted to confirm these results.

SUPPLEMENTARY DATA

Supplementary data are available at the *Journal of Radiation Research* online.

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CONFLICT OF INTEREST

None of the authors has any conflicts of interest to declare.

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