Original Article

Radiation therapy for pelvic recurrent colorectal or gynecological cancer: is whole pelvic irradiation necessary?

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Background: Preoperative whole pelvic radiation therapy (RT) is used commonly for rectal cancer and is the standard field postoperatively in gynecological cancer. However, the ideal field (local *vs.* whole pelvis) has not been determined for local recurrence of these cancers.

Methods: We retrospectively reviewed the data for 52 patients who developed local tumor recurrence of rectal or gynecological cancer treated from 2013 to 2021. The initial treatment for all patients was total excision of the primary tumors without radiation therapy. Radiation therapy targets were surgical stumps, perianastomosis sites, and pelvic lymph nodes, classified according to the pelvic nodal volume atlas for radiation therapy. Patients were divided into the local recurrent tumor only radiation therapy group and the whole pelvis radiation therapy group. Whole pelvis radiation therapy included the common iliac lymph nodes or prophylactic lymph nodes below the L5/S1 junction. We recorded second recurrence after RT and the affected site(s) in each group. We also compared disease-specific survival using uni- and multivariate analyses.

Results: We found no significant differences between the groups regarding second recurrence or regarding the site(s) of recurrence. We also found no significant differences in disease-specific survival between the two RT groups. However, patients who did not receive chemotherapy after the initial surgery and before RT had significantly longer survival (P=0.015).

Conclusions: In patients with locally recurrent rectal or gynecological cancer, we found no significant difference in second recurrence or survival between the local tumor only RT field and the whole pelvic RT field.

Keywords: Radiation therapy (RT); pelvic recurrent tumor; colorectal cancer; gynecological cancer; whole pelvic radiation field

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Introduction

Since total mesorectal excision (TME) has become the standard of care for treating rectal cancer, the postoperative local recurrence (LR) rate of rectal cancer has decreased to 11.5–12.6% (1,2). The postoperative LR rate of uterine endometrial cancer ranges from 14% to 18% (3,4), while the LR rate for uterine cervical cancer after surgery or radiation therapy (RT) ranges from 7.2% to 12.5% (5,6). The National Comprehensive Cancer Network guidelines recommend RT as a treatment for LR (7-9). A whole pelvic radiation field, which includes the prophylactic lymph node (LN) regions, is the major field for preoperative RT for

rectal cancer and the standard field for postoperative RT for endometrial and cervical cancers (10-13). However, no RT fields have been identified for RT for LR. The significance of covering the whole pelvic radiation field, including the prophylactic LN regions, is unclear. Additionally, the frequency of second LR in out-field portions of the pelvis after RT is delivered to an RT field that includes the local recurrent tumor only, without the prophylactic LN regions, is unknown. Recently, pelvic RT fields for colorectal or gynecological cancer have been determined using definitions presented in the pelvic nodal volume atlas (14-16). In the present study, local recurrent tumor locations were meticulously classified according to the definitions presented in the atlas, and sites of second LR after RT were compared between RT with an RT field including only the local recurrent tumor, and RT with a whole pelvic radiation field. To our knowledge, this is the first study comparing these RT fields in patients with second LR after RT. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-2950/rc).

Methods

We retrospectively reviewed the data for 52 patients with pelvic local recurrent tumor of colorectal or gynecological cancer treated with RT between 2013 and 2021. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Institutional Review Board of Nihon University School of Medicine (No. RK-211109-6). Written informed consent for publication was obtained from the patients before RT. As initial treatment, all patients underwent total excision of the primary tumors, only, and did not receive RT. Only one patient with sigmoid colon cancer was suspected to have residual tumors at the perianastomosis site during the initial surgery and included this study. Regarding local recurrent tumor locations, the RT targets of stumps, perianastomosis sites, and pelvic LNs were meticulously classified according to definitions presented in the pelvic nodal volume atlas for RT (14-16). The location of local recurrent tumors in mesorectal LNs after TME of rectal cancer was defined as the area where the mesorectum was located before surgery. When local recurrent tumors invaded the surrounding organs, the surrounding organs were also included in the RT targets. We divided the RT fields into two groups: the local recurrent tumor only group and the whole pelvis group, which included the common iliac LNs or prophylactic LN regions below the L5/S1 junction. The gross tumor volume (GTV) was defined as the local recurrent tumor, and the planned target volume constituted at least a 5-mm margin around the GTV. All patients were irradiated using three-dimensional conformal RT. In patients in the local recurrent tumor only group, the presence of concurrent other pelvic LN metastases outside the RT field was defined as concurrent other site metastasis at RT. Local tumor response after RT was evaluated according to the Response Evaluation Criteria in Solid Tumors (17).

Statistical methods

SPSS version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Univariate analysis using Pearson's χ^2 test was performed to analyze the presence or absence of a second recurrence after RT and the sites of the second recurrence in the two RT field groups. The Kaplan-Meier method was used to calculate disease-specific survival (DSS) from the date of RT completion. Differences in DSS between subgroups were analyzed using the univariate log-rank test and a multivariate Cox proportional hazard model for the following patient characteristics: age (< median *vs.* ≥ median), primary tumor site (colorectal *vs.* gynecological), days from initial surgery to RT (< median *vs.* ≥ median), chemotherapy between the initial surgery and RT (yes *vs.* no), concurrent other site metastasis at RT (yes *vs.* no), Eastern Cooperative Oncology Group (ECOG) performance status at RT (0–1 *vs.* ≥2), RT field group (local recurrent tumor only *vs.* whole pelvis), and chemotherapy after RT (yes *vs.* no). Differences with P values <0.05 were considered statistically significant.

Results

Patient characteristics

The clinical data of all 52 patients are summarized in *Table 1*; 17 (32.7%) were male, and 35 (67.3%) were female. The age at RT initiation ranged from 32 to 88 years (median, 67 years). The most common site of local recurrent tumors targeted by RT was the region including stumps in 22 patients (42.3%), followed by the region including mesorectal LNs in 7 patients (13.5%). The most common primary tumor was rectal cancer, which was found in 18 patients (34.6%), followed by colon and uterine endometrial cancers in 10 patients (19.2%). One

Table 1 Characteristics of patients undergoing radiation therapy for pelvic local recurrent tumors (n=52)

Characteristics	RT field group	
	Local recurrent tumor only (n=42)	Whole pelvis (n=10)
Age at the time of RT, median years [range]	67 [32–88]	67 [32–88]
Sex, n (%)		
Male	15 (35.7)	2 (20.0)
Female	27 (64.3)	8 (80.0)
RT target local recurrent tumor location, n (%)		
Stump	9 (21.4)	3 (30.0)
Stump + mesorectal LN	1 (2.4)	1 (10.0)
Stump + obturator LN	0 (0.0)	1 (10.0)
Stump + presacral LN	1 (2.4)	0 (0.0)
Stump + obturator + iliac LN	1 (2.4)	0 (0.0)
Stump + iliac LN	2 (4.8)	1 (10.0)
Stump + inguinal LN	1 (2.4)	0 (0.0)
Stump + external urethral orifice	1 (2.4)	0 (0.0)
Peri-anastomosis	4 (9.5)	1 (10.0)
Peri-anastomosis + presacral LN	1 (2.4)	0 (0.0)
Mesorectal LN	2 (4.8)	0 (0.0)
Mesorectal + obturator LN	1 (2.4)	0 (0.0)
Mesorectal + obturator + iliac LN	1 (2.4)	0 (0.0)
Mesorectal + obturator + iliac LN + uterus	0 (0.0)	1 (10.0)
Mesorectal LN + rectum	1 (2.4)	0 (0.0)
Mesorectal LN + rectum + uterus	1 (2.4)	0 (0.0)
Presacral LN	4 (9.5)	0 (0.0)
Presacral LN + ischiorectal fossa	1 (2.4)	0 (0.0)
Presacral + iliac LN	1 (2.4)	0 (0.0)
Obturator + iliac LN	3 (7.1)	1 (10.0)
Obturator + iliac LN + bladder	1 (2.4)	0 (0.0)
Iliac LN	3 (7.1)	1 (10.0)
Inguinal LN	2 (4.8)	0 (0.0)
Primary tumor site, n (%)		
Rectum	15 (35.7)	3 (30.0)
Colon	8 (19.0)	2 (20.0)
Uterine endometrium	9 (21.4)	1 (10.0)
Uterine cervix	6 (14.3)	3 (30.0)
Vulva	2 (4.8)*	1 (10.0)
Ovary	2 (4.8)	0 (0.0)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	RT field group	
	Local recurrent tumor only (n=42)	Whole pelvis (n=10)
The days from initial surgery to RT, median days [range]	559 [51–3,748]	704 [149–2,231]
Chemotherapy between initial surgery and RT, n (%)		
Yes	29 (69.0)	6 (60.0)
No	13 (31.0)	4 (40.0)
Concurrent other site metastasis at RT, n (%)		
Yes	19 (45.2)	1 (10.0)
No	23 (54.8)	9 (90.0)
ECOG performance status at RT, n (%)		
0–1	35 (83.3)	8 (80.0)
2	5 (11.9)	2 (20.0)
3	2 (4.8)	0 (0.0)
Purpose of RT, n (%)		
Pain relief	16 (38.1)	4 (40.0)
Hemostasis	4 (9.5)	0 (0.0)
Leg edema release	2 (4.8)	1 (10.0)
No symptom	20 (47.6)	5 (50.0)
RT field group and total median dose in Gy (range), n (%)		
Local tumor only, 50.4 (30.0–66.0)	40 (95.2)	–
Local tumor only + vaginal BT boost, 45.0 (40.0–50.0) + 10.0	2 (4.8)	–
Whole pelvis, 50.0 (45.0–50.4)	–	1 (10.0)
Whole pelvis + EBRT boost, 45.0 (36.0–50.4) + 10.0 (6.0–16.2)	–	7 (70.0)
Whole pelvis + vaginal BT boost, 50.2 (50.0–50.4) + 17.0 (10.0–24.0)	–	2 (20.0)
Concurrent chemotherapy at RT, n (%)		
Yes	16 (38.1)	4 (40.0)
No	26 (61.9)	6 (60.0)
Chemotherapy after RT, n (%)		
Yes	22 (52.4)	7 (70.0)
No	20 (47.6)	3 (30.0)

*, including one extramammary Paget's disease. RT, radiation therapy; LN, lymph node; ECOG, Eastern Cooperative Oncology Group; EBRT, external beam radiation therapy; BT, brachytherapy.

patient with inguinal LN metastases from ovarian cancer treated with RT was reported before (18). The days from initial surgery to RT ranged from 51 to 3,748 days (median, 567 days). Chemotherapy was administered between the initial surgery and RT in 35 patients (67.3%) and 29 patients (55.8%) received adjuvant chemotherapy after initial surgery because of high risk of recurrence such as LN metastasis. Nine patients received bevacizumab between the initial surgery and RT and five patients received bevacizumab after RT. Concurrent other site metastasis at

Table 2 Treatment outcome after radiation therapy for pelvic recurrent tumors

Parameter	Number (%)
Tumor response	
Complete response	15 (28.8)
Partial response	3 (5.8)
Stable disease	18 (34.6)
Progressive disease	16 (30.8)
Abscess formation*	5 (9.6)
Symptom relief (n=27)	
Complete relief**	2 (7.4)
Partial relief	19 (70.4)
No relief	6 (22.2)

*, five patients developed progressive disease with abscess formation; **, both patients achieved hemostasis.

RT occurred in 20 patients (38.5%). The most common purpose of RT was local control of asymptomatic LR in 25 patients (48.1%), followed by pain relief in 20 patients (38.5%). Regarding the RT field groups, 42 patients (80.8%) received irradiation to the local recurrent tumors only, and 10 patients (19.2%) received irradiation to the whole pelvis. This study was retrospective, so no rationale of selection radiation field was ruled. Regarding the RT total dose, external beam RT (EBRT) at a median dose of 50.4 Gy was delivered to 40 patients in the local recurrent tumor only group, while EBRT at a median dose of 45.0 Gy with a vaginal brachytherapy (BT) boost of 10 Gy was delivered to the stumps of endometrial carcinoma in 2 patients. In the whole pelvis group, EBRT at a dose of 45.0 Gy was delivered to one patient, EBRT at a median dose of 45.0 Gy with a median EBRT boost of 10.0 Gy was delivered to seven patients, and EBRT at a median dose of 50.2 Gy with a median vaginal BT boost of 17.0 Gy was delivered to the stumps of cervical carcinoma or the stumps plus obturator LNs in two patients, respectively. Concurrent chemotherapy during RT was administered to 10 patients (19.2%).

Local response and symptom relief

The tumor local response after RT was evaluated by computed tomography (CT) at a median of 402 days (range, 1–2,572 days) from the date of RT completion. An overall response was observed in 18 (34.6%) patients, and a complete response was observed in 15 (28.8%) patients. Progressive disease was observed in 16 patients (30.8%), among whom 5 (9.6%) showed abscess formation on CT (*Table 2*). Abscess formation was observed in all patients with locally recurrent colorectal cancer (three patients with colon cancer and two patients with rectal cancer). In three of the five patients received irradiation to the local recurrent tumors only, and the other two patients received irradiation to the whole pelvis. RT was delivered at a total dose of 30–61.2 Gy, while tumors were irradiated with 1.8–3 Gy per fraction. In one of the five patients, the rectum was included in the RT targets because rectal invasion was suspected before RT. Three of the five patients with abscess formation received anti-vascular endothelial growth factor agent. Two patients received bevacizumab before or after RT and one received aflibercept with and after RT. Two patients with stable disease underwent total excision of local recurrent tumors after RT. Among 27 symptomatic patients at the start of RT, 2 (7.4%) experienced complete relief, and hemostasis was achieved in all patients. Partial symptom relief was achieved in 19 (70.4%) patients (*Table 2*).

Acute toxicity

Regarding grade ≥3 RT-related toxicities (National Cancer Institute Common Terminology Criteria for Adverse Events 5.0) (19), hematological toxicity was observed in only one patient.

Second recurrent site after RT, and survival

The second recurrence after RT delivered to the first local recurrent tumors was evaluated using CT, in principle which was performed to evaluate the local responses after RT. A second recurrence after RT delivered to the first local recurrent tumor was observed in 27 patients (51.9%). The most common site of second recurrence was extra-pelvic metastasis in 13 patients (25.0%). Among 42 patients in the local recurrent tumor only group, 12 (28.6%) had new pelvic LN recurrence. Among 10 patients in the whole pelvis group, 2 (20.0%) had new pelvic LN recurrence. In the local recurrent tumor only group, 9 patients (21.4%) had new extra-pelvic metastatic recurrence only. In the whole pelvis group, 4 patients (40.0%) had new extra-pelvic metastatic recurrence only. No significant differences in the presence or absence of a second recurrence as well as the sites were observed between the two RT field groups (*Table 3*). In the local recurrent tumor only group, the cumulative

Table 3 Second recurrent site after radiation therapy for pelvic recurrent tumors and univariate analyses of the associations between recurrence and the RT field

Second recurrent site	RT field group, n (%)		P value
	Local recurrent tumor only (n=42)	Whole pelvis (n=10)	
Other pelvic LN only	4 (9.5)	0 (0.0)	0.310
Presacral LN	1 (2.4)		
Iliac LN	2 (4.8)		
Mesorectal LN	1 (2.4)		
Extra pelvic metastasis only	9 (21.4)	4 (40.0)	0.223
Other pelvic LN + extra pelvic metastasis	8 (19.0)	2 (20.0)	0.945
None	21 (50.0)	4 (40.0)	0.569

RT, radiation therapy; LN, lymph node.

Table 4 Univariate and multivariate analyses of the predictors of disease-specific survival after radiation therapy for pelvic recurrent tumors

Prognostic factor	Characteristics	Univariate analysis	Multivariate analysis	
		P value	HR (95% CI)	P value
Age at RT	<67 *vs.* ≥67 years	0.105	0.441 (0.195–0.988)	0.049*
Primary tumor site	Colorectal *vs.* gynecological	0.083	4.253 (1.143–15.831)	0.031*
Days from initial surgery to RT	<567 *vs.* ≥567 days	0.567	0.356 (0.075–1.682)	0.192
Chemotherapy between initial surgery and RT	Yes *vs.* no	0.015*	4.420 (1.073–18.206)	0.040*
Concurrent other site metastasis at RT	Yes *vs.* no	0.000431*	6.059 (2.163–16.968)	0.001*
ECOG performance status at RT	0–1 *vs.* 2–3	0.093	1.986 (0.700–5.640)	0.197
RT field group	Local recurrent tumor only *vs.* whole pelvis	0.745	2.695 (0.892–8.145)	0.079
Chemotherapy after RT	Yes *vs.* no	0.330	0.377 (0.129–1.098)	0.074

*, significant difference between the groups (P<0.05). CI, confidence interval; RT, radiation therapy; ECOG, Eastern Cooperative Oncology Group.

DSS rates were 62.1% [standard error (SE) ±7.8%] 1 year after RT and 43.9% (SE ±8.3%) 3 years after RT. In the whole pelvis group, the cumulative DSS rates were 80.0% (SE ±12.6%) 1 year after RT and 40.0% (SE ±15.5%) 3 years after RT. *Table 4* lists the results of univariate and multivariate analyses for associations between the patients' characteristics and prognosis. No significant differences in DSS were observed between the two RT field groups (*Table 4*). Multivariate analyses identified gynecological cancer, no chemotherapy between initial surgery and RT, and no concurrent metastasis to other sites at RT as significant factors for favorable DSS (*Table 4*). *Figures 1-3* summarize the comparisons of DSS between the local recurrent tumor only group and whole pelvis group; chemotherapy between initial surgery and RT (yes *vs.* no); and concurrent other site metastasis at RT (yes *vs.* no).

Discussion

Postoperative LR of rectal cancer has been treated with RT for many years. In the past, the RT field was the whole pelvis, which included prophylactic LN regions centered on two parallel opposite anteroposterior and posteroanterior standard pelvic fields (20,21). In-field second LR after RT was observed in 56.6% of patients, in one study (20). The RT field for postoperative LR of uterine endometrial cancer

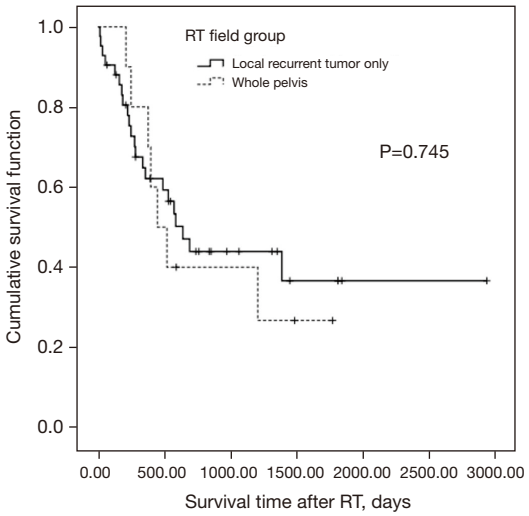

Figure 1 Kaplan-Meier survival curves for patients undergoing radiation therapy for the local recurrent tumor only *vs.* the whole pelvis. The difference between the groups was not statistically significant (P=0.745).

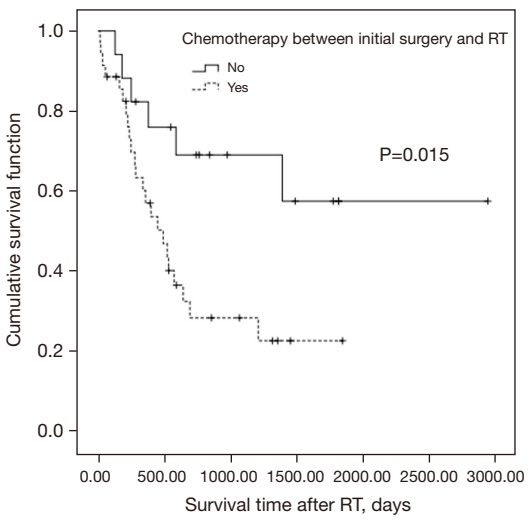

Figure 2 Kaplan-Meier survival curves for patients treated with or without chemotherapy between the initial surgery and radiation therapy (yes *vs.* no). Survival was significantly longer in patients who did not receive chemotherapy (P=0.015). RT, radiation therapy.

is also the whole pelvis, including the prophylactic LN regions, and in some patients, a vaginal BT boost is often combined with RT (22-24). Studies have reported that in-field second LR after RT was observed in 7.1–15.1% of patients (23,24). In a study that included patients receiving

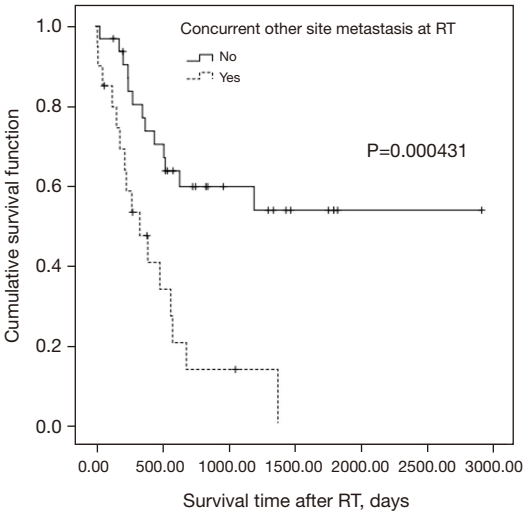

Figure 3 Kaplan-Meier survival curves for patients with or without concurrent other site metastasis at radiation therapy. Survival was significantly longer in patients without concurrent other site metastasis at RT (P=0.000431). RT, radiation therapy.

vaginal BT with and without whole pelvic RT, pelvic progressive disease was observed in 52.1% of the patients after RT (22). In contrast, few studies have evaluated second LR after RT in patients for which RT was delivered to fields that included local recurrent tumors only instead of the whole pelvic radiation field. In the present study, most patients received irradiation to an RT field that included local recurrent tumors only, and 28.5% of the patients in the local recurrent tumor only group had other pelvic LN recurrences. In addition, we confirmed for the first time that no significant differences were observed regarding the presence or absence of second recurrence, second recurrent sites, or DSS between the local recurrent tumor only group and the whole pelvis group. One limitation of this study was that the number of patients treated with whole pelvis was small. The extension of RT field to the pelvic nodes may be detrimental for the patients treated with palliative intent.

Because of recent advances in RT, intensity-modified RT (IMRT) delivered to the whole pelvis to reduce the toxicity has been reported, including the preoperative rectal cancer or local recurrent rectal cancer and prophylactic LN regions (25,26). When IMRT was administered with concurrent chemotherapy to the local recurrent rectal cancer, the local control rate (combined complete and partial responses) was 46.5% (26). In the present study, the local control rate (combined complete and partial responses) was 34.6%, which was lower than the rate mentioned

above. This appears to be attributable to the following reasons: the present study included many patients with LR with concurrent metastasis to other sites at RT. In many patients, RT was administered at palliative doses to achieve symptom relief instead of at definitive RT doses, and most patients received RT without concurrent chemotherapy. Local recurrent tumors of colorectal or gynecological cancer are refractory to RT, which is explained by the more hypoxic nature of local recurrent tumors compared with primary tumors (27). In the present study, DSS was longer in patients who did not receive chemotherapy between the initial surgery and RT than in those who received RT after chemotherapy. This suggests that chemotherapy might have caused local recurrent tumors to become more hypoxic.

Recent reports have described stereotactic body RT (SBRT) or carbon ion RT administered at an increased RT dose per fraction to irradiate local tumors only at the highest RT dose possible, in patients without concurrent metastasis to other sites at RT. These therapies result in favorable treatment outcomes as indicated by the local control rate of 64.5–88.0% (28-30). In comparison, the present study reported a 3-year DSS rate of 40.0–43.9%, which was better than the rate of 27–36.5% in previous reports of IMRT and SBRT (26,28). This suggests that conventional EBRT may be sufficient to affect the survival rate in LR. In SBRT at a high RT dose per fraction, toxicities, such as colorectal perforation and rectovaginal fistula have been reported in 13.0–14.3% of patients (28,29). In the present study, as local recurrent tumors proliferated after RT, abscess formation was observed in 9.6% of the patients. Because the total RT dose delivered to these patients was not as high as that with SBRT, abscess formation was presumably caused by colorectal perforation owing to invasion of proliferating local recurrent tumors rather than because of toxicity. All patients with abscesses had locally recurrent colorectal cancer. Thus, caution should be exercised regarding colorectal perforation if local recurrent tumors proliferate after RT in patients who undergo intestinal tract resection at the initial surgery. In the future, we will examine abscess formation after RT in patients with local recurrent tumors who receive RT and we will also investigate the optimal dose of conventional EBRT for local recurrent tumors in patients with concurrent metastasis at other sites at RT.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-2950/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-21-2950/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-2950/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Institutional Review Board of Nihon University School of Medicine (No. RK-211109-6). Written informed consent for publication was obtained from the patients before radiation therapy.

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