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FULL PAPER

Acute anal toxicity after whole pelvic radiotherapy in patients with asymptomatic haemorrhoids: identification of dosimetric and patient factors

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Objective: Patients with asymptomatic haemorrhoids are known to be less tolerant of radiation doses lower than known tolerance doses. In the present study, the authors sought to identify the risk factors of acute haemorrhoid aggravation after whole pelvic radiotherapy (WPRT).

Methods: The records of 33 patients with cervical, rectal or prostate cancer with asymptomatic haemorrhoids, which were confirmed by colonoscopy before the start of radiotherapy (RT), were reviewed. Acute anal symptoms, such as anal pain and bleeding, were observed up to 1 month after RT completion. Dosimetric and patient factors were analysed, and subgroup analyses were performed.

Results: The median induction dose for acute anal symptoms was 34.1 Gy (range, 28.8–50.4 Gy). Post-operative treatment intent showed more acute anal

toxicity of patient factors ($p = 0.04$). In subgroup analysis, post-operative treatment intent and concurrent chemoradiotherapy were found to be related to acute anal symptoms ($p < 0.01$). Of the dosimetric factors, V_{10} tended to be related to acute anal symptoms ($p = 0.08$).

Conclusion: This study indicates that asymptomatic haemorrhoid may deteriorate after low-dose radiation and that patient factors, such as treatment intent and concurrent chemotherapy, probably influence anal toxicity. In patients with asymptomatic haemorrhoids, WPRT requires careful dosimetry and clinical attention.

Advances in knowledge: The tolerance of anal canal tends to be ignored in patients with pelvic cancer who are undergoing WPRT. However, patients with asymptomatic haemorrhoids may be troubled by low radiation doses, and further studies are required.

Radiotherapy (RT) is widely used for cancer treatment along with surgery and chemotherapy.^{1–5} In particular, whole pelvic RT (WPRT) plays an important role in the locoregional control of pelvic lesions in cervical, rectal and prostate cancer. Although RT is an effective anticancer treatment, it can induce complications in normal organs. There are a lot of studies about radiation tolerance doses in normal organs.^{6–8}

Intestinal problems are common complications of WPRT, whereas severe complications, such as small bowel perforation, are rare.^{9,10} On the other hand, acute anal complications, such as anal pain or bleeding, tend to be ignored because of their lower severities. However, acute anal toxicity is a painful, intractable complication. Although most acute anal problems improve spontaneously after RT completion, they are difficult to resolve during RT and result in complaints from many patients. WPRT is usually administered at doses ≤ 50 Gy, that is, at doses generally

considered safe for the anal canal,¹¹ but when patients have haemorrhoids, RT-induced anal toxicity may become problematic.

Haemorrhoids are very common and the incidence of asymptomatic haemorrhoids is high.¹² If a patient has haemorrhoids before RT, in many institutions, an anal block is used empirically. Most clinicians expect anal toxicity in patients with haemorrhoids following RT, but published studies on the topic are rare.

In the present study, we sought to identify the risk factors of acute anal toxicity following WPRT in patients with pelvic cancer with asymptomatic haemorrhoids.

METHODS AND MATERIALS

Patients

We retrospectively analysed the archived records of 33 patients with asymptomatic haemorrhoids who underwent WPRT

between 2008 and 2014. Patients with cervical, rectal and prostate cancer undergoing WPRT were included, whereas patients with rectal cancer with involvement at <5 cm from the anal verge were excluded. Patients who underwent additional RT, such as intracavitary brachytherapy or a lymph node boost after WPRT, were not excluded if the irradiated field did not include the anal canal. Before RT, asymptomatic haemorrhoids were confirmed by colonoscopy. Acute anal symptoms, such as anal pain and bleeding, were observed up to 1 month after RT completion.

Radiotherapy

RT was delivered using a 21 EX unit (Varian® Medical Systems, Palo Alto, CA) and with 6- or 10-MV X-rays. Patients with cervical or prostate cancer were administered WPRT using the box technique (Figure 1). Patients with rectal cancer were treated using the three-field technique (bilaterally and posteroanteriorly), and planning was conducted with the aid of CT simulation (Asteion CT scanner; Toshiba Medical Systems, Tokyo, Japan) using 3-mm slices. WPRT was delivered at a median level of 50.4 Gy (range, 45.0–55.8 Gy) at 1.8 Gy per fraction. The lower margin of RT fields was the inferior border of the ischial tuberosity or obturator foramen, depending on staging and tumour extension. The posterior margin was set from the S2/S3 vertebra to behind the sacrum, depending on the primary disease and tumour extension. The perineal area and femoral

head were blocked in RT fields. After WPRT, seven patients underwent high dose rate intracavitary brachytherapy, and two patients received an intensity-modulated RT (IMRT) boost to the cervical mass. Intracavitary brachytherapy was applied at a point A dose of 25 Gy (5 Gy per fraction, twice weekly), IMRT boost doses were 23.4 and 19.8 Gy in two patients. A parametrial boost was performed in five patients at a median dose of 9 Gy (range, 5.4–10.0 Gy). Three patients with prostate cancer received an IMRT-delivered prostate or tumour bed boost at a median level of 24.2 Gy (range, 14.0–24.2 Gy). In these patients, the anal canal was not irradiated by intracavitary brachytherapy or by IMRT.

Analysis of dosimetric/patient factors

In each case, the anal canal, which was defined from the anal verge to 3-cm superior area, was delineated in planning CT scans, and its volume was calculated. The location of the anal verge was defined using the last image of the external sphincter muscle in planning CT images. Dose-volume histograms (DVHs) of the anal canal were obtained using an Eclipse™ treatment planning system (Varian Medical Systems). The V_{dose} was defined as the anal canal volume that received at over the dose, and V_{10} – V_{45} values were calculated from DVHs. Other dosimetric factors such as the mean anal canal dose and anal canal volume were also analysed. Various patient factors were analysed, and subgroup analyses were also performed.

Figure 1. Three-dimensional whole pelvic radiotherapy planning. A, anterior; F, foot; H, head; L, left; P, posterior; R, right.

Statistical analysis

The Student's *t*-test was used to analyse the relations between acute anal symptoms and dosimetric factors. Pearson's χ^2 test and Fisher's exact test were used to analyse patient and dosimetric factors. *p*-values of <0.05 were considered statistically significant. The statistical analysis was performed using SPSS® v. 18.0 (SPSS Inc., Chicago, IL).

RESULTS

The median age of the 33 patients was 67 years (range, 33–82 years), and there were 12, 18 and 3 patients with cervical, rectal and prostate cancer respectively. 14 patients were post-operative treatment intent, and 19 patients were definitive or pre-operative treatment intent. RT alone or concurrent chemoradiotherapy (CCRT) were administered to 14 and 19 patients, respectively. Seven patients with cervical cancer undergoing CCRT received weekly concurrent cisplatin (40 mg m^{-2}) for a total of four to six cycles. Of the 12 patients with rectal cancer undergoing CCRT, 11 patients were treated with 5-fluorouracil (400 mg m^{-2}) and leucovorin (20 mg m^{-2}) every 4 weeks.

Induction radiation dose and acute anal toxicity

Of the 33 patients, 14 (42.4%) patients had acute anal symptoms following WPRT. The median induction dose for the initiation of acute anal symptoms was 34.1 Gy (range, 28.8–50.4 Gy). Induction doses used in each patient are illustrated in Figure 2. Of the 14 patients with acute anal symptoms, 10 (71.4%) patients had an induction dose of ≤ 36 Gy and 4 (28.6%) patients had an induction dose of >36 Gy. The median time to the initiation of acute anal symptoms was 24 days (range, 21–36 days) after RT start. All patients had anal pain, and anal bleeding was accompanied in five patients. Haemorrhoid prolapse occurred in two patients.

Analysis of patient factors

Post-operative treatment intent was the only significant patient factor identified ($p = 0.04$). Patients (9/14, 64.3%) undergoing post-operative RT showed more acute anal symptoms than did patients (5/19, 26.3%) undergoing definitive/pre-operative RT. At an age of 60 years or less CCRT tended to be associated with the development of anal symptoms ($p > 0.05$, Table 1). However, by subgroup analysis, treatment intent, age and CCRT were found to be significantly correlated with acute anal symptoms (Table 2).

Analysis of dosimetric factors

The average mean anal canal dose was 32.1 Gy (range, 2.9–52.4 Gy). Although patients with anal symptoms had higher dosimetric factor values than did patients without anal symptoms, differences were not significant (Table 3). V_{10} tended to be associated with the development of acute anal symptoms ($p = 0.08$). In detailed analysis by irradiated anal volume, patients with anal symptoms showed non-significantly higher hazard ratios for almost all dosimetric factors (Table 4).

DISCUSSION

Many patients undergoing WPRT experience acute anal toxicity.¹³ However, few studies have addressed this topic, because acute anal

toxicity usually resolves spontaneously. At the onset of this study, we considered that acute anal toxicity was probably related to haemorrhoids. In the present study, we attempted to identify the risk factors of acute anal symptoms in patients with cervical, rectal and prostate cancer with asymptomatic haemorrhoids.

Radiation-induced proctitis is defined as damage and inflammation to the lower colon following RT.¹⁴ On the other hand, haemorrhoids are usually observed in the anal canal 3 cm distal from the anal verge. However, radiation-induced proctitis and haemorrhoid aggravation are difficult to differentiate. Acute anal symptoms in patients with asymptomatic haemorrhoids undergoing WPRT are considered to be owing to haemorrhoid aggravation rather than radiation-induced proctitis, because the symptoms of acute radiation-induced proctitis are commonly diarrhoea and defecation urgency,¹⁴ whereas those of haemorrhoids are anal pain and bleeding. Main symptoms are different between acute radiation-induced proctitis and haemorrhoid aggravation. Of course, anal bleeding and painful defecation are common symptoms in chronic radiation-induced proctitis. To avoid confusion about terms, although it is not a definite term, we used the term “acute anal symptoms” in the present study.

It is known that radiation doses of 45–55 Gy delivered in fractions of 1.8–2.0 Gy are safe for the anal canal.¹¹ In the present study, acute anal symptoms after WPRT occurred in about 40% of patients, and the induction doses for anal symptoms were usually between 30 and 40 Gy with a median of 34.1 Gy. This implies that haemorrhoids can considerably decrease the tolerance level of the anal canal. We expected to find strong relationships between acute anal symptoms and dosimetric factors, but we found stronger relationships with patient factors. Of these factors, CCRT, post-operative treatment intent and age 60 years or less tended to be related to the development of acute anal toxicity. It is difficult to explain the inverse relation between age and symptom development identified by subgroup analysis, although it might reflect higher pain tolerance in older patients. Post-operative

Figure 2. Radiation doses initiating acute anal symptoms in patients (dotted line: median dose).

Table 1. Acute anal symptoms and patient factors

Variable	<i>n</i>	Anal symptoms	Hazard ratio	95% confidence interval	<i>p</i> -value
Age (years)					
≤60	12	8 (66.7%)	5.0	1.1–23.1	0.07
>60	21	6 (28.6%)			
Sex					
Male	16	7 (43.8%)	1.1	0.3–4.4	0.88
Female	17	7 (41.2%)			
Post-operative radiotherapy					
Yes	14	9 (64.3%)	5.0	1.1–22.5	0.04
No	19	5 (26.3%)			
Chemotherapy					
Concurrent	19	10 (52.6%)	2.8	0.6–12.1	0.17
Radiotherapy alone	14	4 (28.6%)			
Primary disease site					
Cervix	12	6 (50.0%)	1.6	0.4–6.9	0.55
Rectum	18	7 (38.9%)			

treatment intent and CCRT were significantly related to anal toxicity development ($p < 0.00$). Of the dosimetric factors, only V_{10} tended to be related with acute anal symptoms ($p = 0.08$). Although they were not statistically significant, almost all dosimetric values were higher in patients with anal symptoms.

A small number of reports based on analyses of relations between radiation-induced intestinal complication and dosimetric factors have been issued on intestinal toxicity following RT.^{15–17} Tucker *et al*¹⁷ reported that late rectal bleeding is related to irradiated dose >32 Gy in the rectal wall. Iyengar *et al*¹⁵ found that 40 Gy delivered to $\geq 58\%$ of rectal volume and 30 Gy to $\geq 72\%$ of rectal volume were related to late intestinal toxicity. However, this focus on late complications makes direct comparisons with our findings

difficult. The published study about acute anal symptoms was rare. In our study, although anal symptoms mostly appeared between 30 and 40 Gy, V_{10} showed a stronger relation with acute anal symptoms than V_{30-40} . Furthermore, in almost all patients affected, anal symptoms occurred at similar times after RT commencement, which suggests low radiation doses, such as 10 Gy, aggravate asymptomatic haemorrhoids and that anal symptoms are expressed after a certain time. It is believed that the thinned epithelium of haemorrhoids is easily damaged by RT, and although anal symptoms usually appeared between 30 and 40 Gy in the present study, it appears that doses <30 Gy can induce anal symptoms. To determine the nature of the changes that occur in haemorrhoids, colonoscopy or anoscopy studies are required during the RT period. The present study was conducted using a retrospective approach, and thus, additional examinations were

Table 2. Subgroup analysis of patient factors

Variable	<i>n</i>	Anal symptoms	Hazard ratio	95% confidence interval	<i>p</i> -value
Post-operative intent and CCRT	7	6 (85.7%)	36.0	1.8–718.7	0.00
Without both	7	1 (14.3%)			
Age ≤60 years and CCRT	8	5 (62.5%)	15.0	1.2–185.2	0.04
Without both	10	1 (10.0%)			
Age ≤60 years and post-operative intent	6	5 (83.3%)	27.5	2.0–378.8	0.00
Without both	13	2 (15.4%)			
Post-operative intent, CCRT and age ≤60 years	3	2 (66.7%)	10.0	0.4–250.4	0.13
Without all	6	1 (16.7%)			

CCRT, concurrent chemoradiotherapy.

Table 3. Relationships between acute anal symptoms and dosimetric factors

Parameter	Mean		<i>p</i> -value
	AS (SD)	NAS (SD)	
Anal canal volume (ml)	9.1 (3.1)	9.9 (2.5)	0.44
D_{mean} (Gy)	34.4 (13.1)	30.4 (14.7)	0.56
D_{min} (Gy)	14.2 (16.7)	10.4 (13.8)	0.25
D_{max} (Gy)	48.5 (4.3)	44.2 (11.1)	0.73
V_{10} (%)	81.9 (21.3)	72.1 (33.2)	0.08
V_{20} (%)	74.3 (25.9)	65.8 (35.2)	0.16
V_{30} (%)	65.3 (33.6)	58.8 (36.1)	0.52
V_{40} (%)	58.4 (36.1)	49.9 (35.0)	0.95
V_{45} (%)	37.8 (38.5)	29.1 (34.0)	0.49
V_{10} (ml)	7.5 (3.0)	7.1 (3.6)	0.84
V_{20} (ml)	6.8 (3.1)	6.5 (3.7)	0.77
V_{30} (ml)	5.9 (3.3)	5.8 (3.8)	0.81
V_{40} (ml)	5.3 (3.5)	5.0 (3.7)	0.99
V_{45} (ml)	3.3 (3.5)	3.1 (3.8)	0.84

AS, anal symptoms; D_{max} , maximum dose; D_{mean} , mean dose; D_{min} , minimum dose; NAS, non-anal symptoms; SD, standard deviation; V_{dose} , volume of anal canal receiving the dose.

not performed to confirm haemorrhoid aggravation during RT period in all patients. Furthermore, such examinations may be meaningless from the treatment perspective because the treatment is conservative care. It is only valuable in the view of prevention.

The most obvious limitation of the presented study is the small number of patients enrolled. Nevertheless, we consider the study to be meaningful because it introduces the acute aggravation of asymptomatic haemorrhoids by low-dose radiation. In the patients with cervical cancer, some underwent intracavitary brachytherapy or an IMRT boost to the cervix, and these additional treatments did not include the anal

canal, and thus, these patients were included in the present study.

Our findings indicate that asymptomatic haemorrhoid can be aggravated by low-dose radiation, and thus, careful dosimetry and clinical attention are needed in patients with haemorrhoids undergoing RT. We suggest that a prospective study be undertaken using techniques, such as anoscopy, with a view towards issuing guidelines regarding the differentiation of haemorrhoid aggravation and radiation proctitis. Nowadays, IMRT technique has been tried for WPRT. To prevent anal toxicity, a further study is required on dosimetric comparisons between conventional WPRT and IMRT technique.

Table 4. Dosimetric analysis between acute anal symptoms and irradiated anal volume

Irradiated anal volume	AS	NAS	HR	<i>p</i> -value	AS	NAS	HR	<i>p</i> -value
	V_{10}				V_{20}			
$\geq 1/3$	14/14 (100%)	15/19 (78.9%)	1.9	0.07	13/14 (92.9%)	15/19 (78.9%)	3.5	0.27
$\geq 1/2$	11/14 (78.6%)	15/19 (78.9%)	1.0	0.98	11/14 (78.6%)	14/19 (73.7%)	1.3	0.75
$\geq 2/3$	11/14 (78.6%)	13/19 (68.4%)	1.7	0.52	11/14 (78.6%)	11/19 (57.9%)	2.7	0.21
1	5/14 (35.7%)	5/19 (26.3%)	1.6	0.56	5/14 (35.7%)	4/19 (21.1%)	2.1	0.35
	V_{30}				V_{40}			
$\geq 1/3$	10/14 (71.4%)	14/19 (73.7%)	0.9	0.89	10/14 (71.4%)	12/19 (63.2%)	1.5	0.62
$\geq 1/2$	10/14 (71.4%)	11/19 (57.9%)	1.8	0.42	10/14 (71.4%)	11/19 (57.9%)	1.8	0.42
$\geq 2/3$	10/14 (71.4%)	10/19 (52.6%)	2.3	0.28	6/14 (42.9%)	5/19 (26.3%)	2.1	0.32
1	4/14 (28.6%)	3/19 (15.8%)	2.1	0.38	3/14 (21.4%)	2/19 (10.5%)	2.3	0.39

AS, anal symptoms; HR, hazard ratio; NAS, non-anal symptoms; V_{dose} , volume of anal canal receiving the dose.

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