RESEARCH ARTICLE

Possible Risk Factors Associated with Radiation Proctitis or Radiation Cystitis in Patients with Cervical Carcinoma after Radiotherapy

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Abstract

Radiation proctitis and radiation cystitis are major complications for patients with cervical carcinoma following radiotherapy. In the present study, we aimed to determine the potential risk factors for the development of radiation proctitis and radiation cystitis after irradiation. A total of 1,518 patients with cervical carcinoma received external beam radiotherapy (EBRT) followed by high-dose-rate intracavitary brachytherapy (HDRICB) in our hospital. The incidences of radiation proctitis and radiation cystitis were recorded and associations with different factors (age, time period, tumor stage) were analyzed with χ^2 (chi-squared) and Fisher exact tests. We found that 161 and 94 patients with cervical carcinoma were diagnosed with radiation proctitis and radiation cystitis, respectively, following radiotherapy. The prevalence of Grade I-II radiation proctitis or radiation cystitis was significantly lower than that of Grade III (radiation proctitis: 3.82% vs. 6.76%, $P < 0.05$; radiation cystitis: 2.31% vs. 3.87%, $P < 0.05$) and was significantly enhanced in patients with late stage (IIIb) tumor progression compared to those in early stage (Ib, IIa) ($P < 0.05$). Moreover, the incidence of radiation proctitis and cystitis was not correlated with age or, time period following radiation, for each patient ($P > 0.05$). These observations indicate that a late stage of tumor progression is a potential risk factor for the incidence of radiation proctitis and cystitis in cervical carcinoma patients receiving radiotherapy.

Keywords: Cervical carcinoma - radiotherapy - radiation proctitis - radiation cystitis - risk factors

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Introduction

Cervical carcinoma is a life-threatening health problem, accounting for the death of nearly 500,000 women each year worldwide (Waggoner, 2003; Jemal et al., 2011). Radiotherapy, radical hysterectomy and radio-chemotherapy are recognized as effective treatment options for patients with cervical carcinoma (Landoni et al., 1997; Morris et al., 1999; Rose et al., 1999). High-dose-rate intracavitary brachy therapy (HDRICB) combined with external beam radiotherapy (EBRT) showed various advantages for the management of cervical carcinoma, including elimination of personnel exposure and short treatment time with the possibility of maintaining exact applicator geometry. Therefore, this therapy combination is widely applied in Japan and parts of Europe (Kapp et al., 1997; Mabuchi et al., 2010; Niibe et al., 2010).

A major issue in the management of radiotherapy involves complications secondary to radiation treatment. Radiation therapy for cervical carcinoma has been reported to lead to severe complications in the bladder and the rectum (Montana and Fowler, 1989), which may contribute to the poor prognosis for patients with cervical carcinoma (Toita et al., 1994; Suzuki et al., 2000; Niibe et al., 2006). The optimal radiation dose and schedule has not been well established cervical carcinoma, even though the same dose has been clinically administered for squamous cell carcinoma (67–86 Gy_{10}) with 10 grey (Gy_{10}) as the biological effective dose if α/β is 10 (Nakano et al., 2005). Nevertheless, the potential risk factors of patients with cervical carcinoma for the incidence of radiation proctitis and radiation cystitis after receiving radiotherapy have not yet been fully determined.

In this present study, we retrospectively analyzed 1518 women who recieved radiotherapy for the treatment of cervical carcinoma at the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui in China from February 1993 to July 2009. The prevalence of radiation proctitis and radiation cystitis after receiving radiotherapy was investigated and the underlying risk factors were determined. Our current study may provide valuable insights for predicting and preventing radiation-induced complications of the bladder and rectum in Chinese patients with cervical carcinoma undergoing chemotherapy.

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Table 1. Demographic and Clinical Characteristics of Selected Subjects

Demographic characteristics		Total subjects (n=1518)	
		N	%
Age (years)	<40	264	17.39
	40-60	676	44.53
	>60	578	38.08
Tumor type	Squamous cell carcinoma	1379	90.84
	Adenocarcinoma	87	5.73
	Adenosquamous carcinoma	15	1
	Small cell cervical cancer	21	1.38
	Neuroendocrine carcinoma	16	1.05
Tumor stage	Ib	45	2.96
	IIa	187	12.32
	IIb	509	33.53
	IIIa	354	23.32
	IIIb	423	27.87

Materials and Methods

Subjects

A total of 1518 women who received for the treatment of cervical carcinoma radiotherapy at the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui in China from February 1993 to July 2009 were included. Informed consent was obtained from each patient and the study was approved by the Institutional Review Board (IRB) approval and in accordance with the Declaration of Helskinki. Demographic and clinical characteristics of selected subjects are presented in Table 1. Patient age ranged from 26 to 90 years, with an average age of 57 years. Inclusion criteria were as follows: (1) patients ≤70 years old; (2) initial treatment; (3) no history of pelvic surgery or radiotherapy; and (4) absence of cardio-cerebrovascular disease (5) absence of diabetes or immune system disorders. Exclusion criteria were as follows: (1) multiple metastases; (2) cachexia; and (3) massive effusion in thoracic and abdominal cavity. Follow-up was conducted until July 2011. The follow-up period ranged from 2 to 18 years, with an average period of 10 years.

Radiotherapy procedures

Radiotherapy consisted of EBRT followed by HDRICB at the Department of Radiation Oncology, the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China. During the initial therapy, patients received EBRT at a dosage of 3200-3600 cGy/16-18 f to the whole pelvis via anterior and posterior parallel fields using the 6 MV X-ray mode of the Varian 23EX accelerator (USA). Conventional plans using U-shaped fields or four fields (opposed anterior-posterior and lateral), with care to avoid the urinary bladder and rectum, were generated at a dosage of 1500-1800 cGy for the second stage of radiotherapy. After adequate tumor regression, HDRICB was performed using an Ir-192 remote after-loading technique. The standard prescribed dose for each HDRICB was 500-1000 cGy to Point A. The total prescribed Point A doses ranged from 3000 to 3500 cGy.

Grading criteria for radiation proctitis

Status for radiation proctitis was scored according to the grading scale reported by Esche et al (Esche, Crook, and Horiot, 1987). Briefly, patients with mild radiation proctitis (Grade I) were defined as: Sequelae were not debilitating and lasted less than 6 months or were extremely intermittent. Patients with moderate radiation proctitis (Grade II) were defined as: Sequelae included all those requiring hospitalization, transfusion, or more than 6 months of medical treatment. Patients with severe radiation proctitis (Grade III) were defined as: Sequelae included all fistulas, all conditions requiring surgical correction, and all fatal complications.

Grading criteria for radiation cystitis

The grading system used for radiation cystitis was used based on the criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) (Herrmann, Knorr, and Dorner, 1987). Patients with mild radiation cystitis (Grade I) were defined as: (1) Patients with mild symptoms and signs, including frequent micturition, urgency of urination and urine pain; (2) Cystoscopy examination revealed that the mucosa was cloudy, hyperemic and edema. Patients with moderate radiation cystitis (Grade II) were defined as: (1) Patients, in addition to the above symptoms, complained of repeated hematuresis arising from capillary dilation of the bladder mucosa; (2) Cystoscopy revealed edema of the mucosa with a fibrous membrane, ulcer formation and capillary dilation in a considerable range. Patients with severe radiation cystitis (Grade III) were defined as: Patients with the formation of vesicovaginal fistula.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Science program (SPSS), version 13.0. Comparison of enumeration data was carried out with χ^2 (chi-squared) and Fisher exact tests. A p-value <0.05 was considered statistically significant.

Results

The incidence of radiation proctitis and radiation cystitis in patients with cervical carcinoma following radiotherapy

Among 1518 studied subjects, 161 and 94 patients with cervical carcinoma were diagnosed with radiation proctitis or radiation cystitis, respectively, following radiotherapy (Table 2). The prevalence of Grade I-II radiation proctitis was significantly lower than that of Grade III radiation proctitis (3.82% vs. 6.79%, $\chi^2 = 13.28$,

Table 2. Incidence of Radiation Proctitis or Radiation Cystitis in Patients Following Radiotherapy. Data Were Presented as Number of Cases or Percentages

	Incidence of radiation proctitis (n=1518)		Incidence of radiation cystitis (n=1518)	
	n	%	n	%
Grade I-II	58	3.82	35	2.31
Grade III	103*	6.79*	59*	3.87*
Grade I-III	161	10.61	94#	6.18#

*P < 0.05 compared with Grade I-II; #P < 0.05 compared with the incidence of radiation proctitis

Table 3. Incidence of Radiation Proctitis or Radiation Cystitis in Patients with Different Ages or During Different Time Periods Following Radiotherapy. Data were presented as number of cases (percentage)

			Incidence of radiation proctitis			Incidence of radiation cystitis
			I-II	III	I-III	I-II
Age (years)	≤40	n=264	22 (8.33%)	1 (0.38%)	23 (8.71%)	13 (4.92%)
	>40 ≤60	n=676	71 (10.50%)	2 (0.30%)	73 (10.80%)	39 (5.77%)
	>60	n=578	64 (11.07%)	1 (0.17%)	65 (11.25%)	42 (7.27%)
Periods	1993.2.1-2000.12.31	n=559	65 (11.63%)	2 (0.36%)	67 (11.98%)	43 (7.69%)
	2001.1.1-2005.12.31	n=572	57 (9.97%)	2 (0.35%)	59 (10.31%)	35 (6.12%)
	2006.1.1-2009.7.31	n=387	35 (9.04%)	0 (0)	35 (9.04%)	16 (4.13%)

No significant difference was detected between different groups ($P > 0.05$)

Table 4. Incidence of Radiation Proctitis or Radiation Cystitis in Patients with Different Tumor Stages Following Radiotherapy. Data were presented as number of cases or percentages

	Incidence of radiation proctitis		Incidence of radiation cystitis	
	n	%	n	%
Ib (n=45)	1*#	2.22*#	0*	0*
IIa (n=187)	6*#	3.21*#	7*	3.74*
IIb (n=509)	51**	10.02**	28	5.51
IIIa (n=354)	44	12.43	22	6.21
IIIb (n=423)	59**	13.95**	37	8.75

*$P < 0.05$ compared with IIIb group; #$P < 0.05$ compared with IIIa group; **$P < 0.05$ compared with IIa group

$P < 0.05$). Similarly, the incidence of Grade I-II radiation cystitis was decreased as compared with that of Grade III radiation cystitis (2.31% vs. 3.89%, $\chi^2 = 6.32$, $P < 0.05$).

The prevalence of radiation proctitis and radiation cystitis was not correlated with the age or the time period of patients

We next investigated the potential association between the incidence of radiation proctitis or radiation cystitis with age and the time period of patients. Although the prevalence of radiation proctitis or radiation cystitis was enhanced with the increased age of patients with cervical carcinoma following radiotherapy, a significant difference was not observed (Table 3). Likewise, disease incidence was slightly decreased in the recent decade, but no statistical difference was found in regard to a decrease of radiation proctitis or cystitis (Table 3). These results indicated that the incidence of radiation proctitis and radiation cystitis was not associated with the age or time period of patients with cervical carcinoma following radiotherapy.

The prevalence of radiation proctitis and radiation cystitis was associated with the tumor stage of patients

As revealed by Table 4, when patients were subgrouped by tumor stage, significant the incidence of radiation proctitis was enhanced in patients with late stage (IIIa, IIIb) tumor progression compared to those in early stage (Ib, IIa) ($P < 0.05$). In addition, the incidence of radiation cystitis was increased in patients with late stage (IIIb)\ tumor progression as compared with patients with early stage (Ib, IIa) tumor progression ($P < 0.05$). These findings demonstrated that the prevalence of radiation proctitis and radiation cystitis was closely associated with the tumor stage of patients following radiotherapy for cervical carcinoma.

Discussion

Cervical carcinoma has been reported to be the third most common cancer and the fourth leading cause of cancer death in women worldwide (Jemal et al., 2011). Combinational therapy of HDRICB and EBRT has been widely used for the treatment of cervical carcinoma (Kapp et al., 1997; Mabuchi et al., 2010; Niibe et al., 2010). However, complications, including radiation proctitis and radiation cystitis, commonly occur following irradiation.

A Japanese retrospective study showed that among Japanese women with severe complications requiring surgical intervention following radiotherapy for cervical carcinoma, 16 patients (8.1%) had severe urologic complications and 26 patients (13.2%) had severe complications of the rectum or intestine (Fujikawa et al., 2001). Moreover, the incidence of spontaneous rupture of the urinary bladder was reported to be 2.0% in Japan (Fujikawa et al., 2001). In China, the incidence of radiation proctitis and radiation cystitis following californium-252 (252Cf) neutron intracavitary brachytherapy (ICBT) combined with EBRT was reported as 7.1% and 6.2%, respectively, for patients with Stage IB to IIIB cervical carcinoma (Lei et al., 2011). Impressive results with acceptable late toxicity can be achieved in the treatment of cancer of the cervix using an ideal combination of EBRT and ICRT (Saibishkumar et al, 2006). A similar follow-up study revealed that among 240 cases of Stage I to Stage III cervical carcinoma, 13.3% and 8.8% patients had severe radiation proctitis and radiation cystitis, respectively, following ICBT combined with EBRT (Yu et al., 2004). A retrospective study patients diagnosed with Stages IB to IVB uterine cervical cancer showed that combined teletherapy along with high dose rate Cobalt -60 brachytherapy (850 cGy/ fraction weekly to Point A for two fractions) led to a slightly higher incidence of Grade 2 radiation proctitis (Pesee et al, 2010). In this present study, we retrospectively analyzed 1518 women who received radiotherapy in our hospital for the treatment of cervical carcinoma. Consistent with previous observations, among the 1518 patients, 10.61% and 6.20% patients were diagnosed with radiation proctitis and radiation cystitis, respectively, following radiotherapy.

Previous studies indicated that an age of >60 years was correlated with a higher rate of rectal morbidity in Korean patients with uterine cervical cancer treated with

EBRT followed by intracavitary irradiation (Kim et al., 2008). This is most likely due to the diminished elasticity of the vaginal walls in these patients, which hinders the optimal site for radiation delivery with maximum sparing of normal tissue. In this present study, no significant differences between the incidences of radiation proctitis or radiation cystitis were attributable to patient age. This discrepancy might be due to the different radiotherapies used in each study. In our study, for older patients, a single radiator duct was utilized and the dose distribution conformed to the shape of the uterus.

Using an in-house scoring system and the French-Italian Glossary (FIG), Kapp and colleagues rated the complications in patients with Stage IB-IVB cervical carcinoma (Kapp et al., 1997). They found that several pretreatment factors influenced the likelihood of complications, including age, marked obesity (Hanks et al., 1983; Combes et al., 1985), previous surgery, history of inflammatory disease (Hanks et al., 1983) and stage (Lanciano et al., 1992). The study demonstrated that only the stage of cervical carcinoma was closely associated with the incidence and severity of radiation proctitis and radiation cystitis by univariate and multivariate analysis. However, the potential influence of tumor stage on the incidence of radiation proctitis and radiation cystitis following radiotherapy has not been clearly illustrated. In this study, we found that the incidence of radiation proctitis was significantly enhanced in patients with late stage (IIIA and IIIB) tumor progression compared to patients with early stage tumor progression (IB, IIA) ($P < 0.05$). Similarly, the incidence of radiation cystitis was increased in the patients with late stage (IIIb) tumor progression as compared with patients with early stage (Ib, IIa) tumor progression ($P < 0.05$). These results were in accordance with previous studies (Kapp et al., 1997). It is possible that limited, moderate or severe radiation proctitis and radiation cystitis in patients with early tumor stage with favorable anatomy permitted optimal site-directed radiation, thus sparing normal tissue.

Uno et al. reported that of 100 patients with Stage IIB and IIIB cervical carcinoma treated with high dose rate intracavitary brachytherapy, 33% and 38% had experienced moderate to severe (Grade 2-4) complications at 3 and 5 years, respectively (Uno et al., 1998). Mean value of depth (D) of 6-Gy isodose volume in patients with and without complication were 51 mm and 46 mm, respectively ($P < 0.05$) (Uno et al., 1998). Moreover, the cumulative point S (2 cm dorsal from the midpoint of the ovoid sources) dose and the single or total point S dose by radiotherapy were significantly higher in patients who developed complication ($P < 0.05$), whereas those factors did not significantly affect the probability of pelvic control (Uno et al., 1998). Consistent with these findings, our results suggest that the high dose area was closely associated with the incidence of complications, especially for patients with late stage tumors. Also, it has been indicated that the biologically effective dose at the bladder reference point may be a significant risk factor for late rectal and bladder morbidity (Kim et al., 2008). Future studies will be conducted to investigate the potential influence of prior surgery, history of inflammatory disease, as well as radiation doses on the incidence of radiation proctitis and radiation cystitis.

Recently, three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) were introduced for the radiotherapy of tumors, such as lung cancer and prostate cancer (Palma et al., 2010). These novel techniques provide greater flexibility in controlling each beam, improving dose distributions, and reducing toxicity (Palma et al., 2010). Compared to conventional radiotherapy, image-guided radiotherapy allows for dose escalation and for the delivery of higher doses to the tumor while maintaining acceptable doses to critical organs at risk (Verellen et al., 2007; Palma et al., 2010). Hence, future studies will also be carried out to compare the incidence of complications, such as radiation proctitis and radiation cystitis, in patients receiving different radiotherapy procedures.

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