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Original Research

Clinical analysis of predisposing factors for radiation enteritis in patients with cervical cancer

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Objective: Radiation enteritis (RE) is one of the most common radiation-induced toxicities in patients with cervical cancer undergoing pelvic radiotherapy. This study aimed to evaluate predisposing factors for RE in patients with cervical cancer. *Methods*: In total, 414 patients with cervical cancer undergoing radiotherapy were retrospectively enrolled from Anhui Provincial Cancer Hospital. We collected data on age; body mass index; International Federation of Gynecology and Obstetrics stage (I–IV); histology; fasting blood glucose levels; chemotherapy regimen; radiation dose; and histories of hypertension, diabetes mellitus, and surgery. Univariate and multivariate Cox regression analyses were used to assess possible predisposing factors for RE. *Results*: Incidences of acute RE (ARE) and chronic RE (CRE) were 65.2% and 13.1%, respectively. No prior surgery, radiation dose $\geq$56 Gy, hypertension, and hyperglycemia were found to be independent risk factors for ARE (95% confidence interval [CI], $p <$ 0.05). Hypertension, diabetes mellitus, and hyperglycemia were independent risk factors for CRE (95% CI, $p \leq$ 0.01). Significantly higher incidences of ARE (90.6% vs. 75.8%, $p <$ 0.001) and CRE (62.5% vs. 21.2%, p = 0.001) were found in patients with diabetes mellitus and poor glucose control. *Conclusions*: To reduce the occurrence of RE in patients with cervical cancer, comorbidities such as diabetes mellitus, hyperglycemia, and hypertension should be controlled, along with consideration of treatment-related factors such as the radiotherapy method and total radiation dose.

Keywords

Cervical cancer; Comorbidity; Predisposing factors; Radiation enteritis; Radiotherapy

1. Introduction

Cervical cancer is one of the most common malignancies in young and middle-aged women and ranks fourth in terms of both morbidity and mortality worldwide [1]. Conventionally, the standard of care for patients with early-stage cervical cancer, including International Federation of Gynecology and Obstetrics (FIGO) stage IB–IIA, is radical hysterectomy and lymph node dissection and/or radiotherapy with/without chemotherapy. For patients with advanced stage cervical cancer, the current management strategy consists of external radiotherapy concurrent with chemotherapy followed by brachytherapy. As a postoperative adjuvant or a definitive treatment, radiotherapy plays a crucial role in the therapeutic strategies for patients with cervical cancer. However, exposure of normal tissue to ionizing irradiation leads to adverse reactions for patients with cervical cancer, which significantly affects their quality of life.

The small intestine is known to be extremely sensitive to irradiation, thought to be due to its capacity of rapid cell proliferation. Radiation enteritis (RE) is defined as radiation-induced intestinal mucositis or injury. RE is typically characterized into two types, acute and chronic. Acute RE (ARE) usually occurs during or within 3 months following radiotherapy and presents with intestinal ailments, such as nausea, vomiting, and diarrhea. Consequently, this may lead to radiation dose reduction and/or interruption. Chronic RE (CRE) can persist or occur over 3 months to decades after radiotherapy, and it entails varying symptoms such as chronic diarrhea, intestinal obstruction, and perforation [2]. Since there are few effective treatments, the prevention of RE and radiation-induced intestinal toxicity is drawing immense attention.

The development and severity of RE have been associated with the total dose of radiation delivered, volume of the irradiated intestine, and treatment method [3]. The use of a "belly board" attempts to minimize the volume of the irradiated intestine by placing patients in the prone position [4]. The use of advanced radiation delivery techniques, such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy, allow for different treatment "shapes" that retain steep dose gradients but have minimal impact on the surrounding normal tissues [5]. Lastly, radiation protectants such as amifostine and probiotics have been proposed as potential radiotherapy adjuvants [6].

Nevertheless, approximately 90% of patients receiving pelvic radiotherapy experience permanent intestinal changes, and 5%–50% of patients with cervical cancer receiving radiotherapy may experience gastrointestinal side effects of radiation [7]. Increasing evidence has shown that the risk of RE depends not only on radiation-related factors but also on patient-related factors including age, surgical history, smok-

ing history, prior pelvic inflammatory disease, and collagen vascular disease [8]. Further investigation into the potential predisposing factors for RE is of high clinical value. Therefore, this retrospective study aimed to evaluate the predisposing factors for RE in patients with cervical cancer receiving radiotherapy.

2. Methods

This study retrospectively collected the medical records of 611 patients with cervical cancer who received radiotherapy in Anhui Provincial Cancer Hospital from July 2019 to August 2020. Patients were followed up until April 2021 when data collection and analysis began. Follow-up information was obtained via inpatient visit or telephone visit. The exclusion criteria were as follows: (1) prior pelvic radiotherapy in other hospitals and (2) the presence of other non-cervical cancers. Data were collected on age, body mass index (BMI), FIGO stage, histological subtype, fasting blood glucose (FBG) levels, hypertension history, diabetes mellitus, history, surgical history, chemotherapy regimen, and radiation dose. All participants were anonymized and recorded by number. The Ethics Committee of Anhui Provincial Cancer Hospital approved the study (No. 2021–FLK–02). The requirement for informed consent was waived due to the retrospective nature of this study.

All patients were treated with radiotherapy, including external-beam pelvic radiotherapy and brachytherapy. External-beam radiotherapy was performed using 6 MV photons via the IMRT technique using an Elekta linear accelerator (Elekta, Stockholm, Sweden). Treatment planning was carried out using the Pinnacle^3 16.2 software (Philips, Fitchburg, USA). The target areas were delineated according to consensus guidelines [9, 10]. Clinical target volume (CTV) comprised the gross tumor (for definitive radiotherapy), entire uterus, parametrium, proximal vagina (vaginal stump for adjuvant radiotherapy), paravaginal tissues, pelvic lymph nodes, and abdominal para-aortic lymphatic drainage areas if necessary. The entire vagina was included when the lesions invaded the lower one-third of the vagina. The planning target volume (PTV) was constructed by uniform expansion of the CTV by 7 mm. The prescription dose was 45–50 Gy for PTV at 1.8–2 Gy per fraction. For enlarged lymph nodes, the radiation dose could be increased to 55–66 Gy using simultaneous integrated boost-IMRT. Radiation treatment was administered five times per week. Dose constraints to normal tissues are as follows: rectum and bladder (volume receiving more than 50 Gy is less than 30% and maximum dose is less than 56 Gy); small bowel (volume receiving more than 45 Gy is less than 195 cm^3 and maximum dose is less than 56 Gy). After external-beam radiotherapy, high-dose-rate afterloading brachytherapy was performed once or twice a week. The prescription dose was 30–35 Gy in 5–6 fractions delivered to point A which is referred to 2 cm up from fornix in the axis of the uterus and 2 cm lateral to the central canal of the uterus. In the case of patients undergoing hysterectomy, a vaginal tampon was used, and the dose was 6–10 Gy in 1–2 fractions. For patients with eccentric large tumors, 3-dimensional computed tomography-guided intracavitary/interstitial brachytherapy was added to boost doses. The concurrent chemotherapy regimen consisted of cisplatin (30–40 mg/m^2) per week over the radiotherapy period. All treatments could be adjusted according to individual patient status.

Measurements of FBG were obtained from the clinical laboratory of Anhui Provincial Cancer Hospital. Peripheral blood was collected 1 week before the initiation of radiotherapy, every 2 weeks during radiotherapy, and 1 month after radiotherapy. We defined hyperglycemia as an FBG level $>$6.1 mmol/L, and diabetes mellitus with poor glucose control as an FBG level $>$6.9 mmol/L in any of the tests.

RE was divided into four grades according to the RTOG and European Organization for Research and Treatment of Cancer (EORTC) scales [11]. In brief, grade 0 is defined as no obvious intestinal symptoms. Grade 1 is defined as increased frequency or change in quality of bowel habits or defecation less than five times per day without requirement of medication. Grade 2 is defined as diarrhea (defecation more than five times per day) requiring parasympatholytic drugs or mucosa discharge/bleeding or rectal/abdominal pain requiring analgesics. Grade 3 is defined as diarrhea requiring parenteral support or obstruction/bleeding requiring surgical treatment. Grade 4 is defined as obstruction or perforation or fistula.

All analyses were performed using SPSS version 20 (IBM, Armonk, NY, USA). The Student's t-test was used to compare mean values, and the chi-square test was used to compare categorical data from two groups. A Cox regression model was used to assess the possible predisposing factors for RE by univariate and multivariate analyses. Hazard ratios and 95% confidence intervals (95% CIs) were estimated. Factors shown to be significant in univariate analysis were entered into multivariate analysis. A two-tailed p value < 0.05 was considered statistically significant.

3. Results

A total of 611 patients with cervical cancer were retrospectively evaluated, and 414 patients met the study criteria, whose characteristics are given in Table 1. The median duration of patient follow-up was 14 months (range, 8–21 months). The median age was 54 years, and the median BMI was 23.4 kg/m^2. Most patients with cervical cancer had squamous cell carcinoma (99%), and four patients had non-squamous cell carcinoma. Among these 414 patients, 87 patients (21.0%) had FIGO stage I, 164 patients (39.6%) FIGO stage II, 144 patients (34.8%) FIGO stage III, and 19 (4.6%) FIGO stage IV (FIGO classification, 2009). There were 62 patients (15%) with a history of hypertension and 65 (15.7%) with diabetes mellitus. A total of 212 patients underwent surgery followed by radiotherapy or chemoradiotherapy, while 202 were treated with definitive radiotherapy

Table 1. Patients' baseline characteristics.

Characteristics	
Age (years)	Median, range: 54, 26–91
BMI (kg/m^2)	Median, range: 23.4, 15.8–37.0
Cell type	N (%)
Squamous cell carcinoma	410 (99.03%)
Non-squamous cell carcinoma	4 (0.97%)
FIGO stage	
I	87 (21.01%)
II	164 (39.61%)
III	144 (34.78%)
IV	19 (4.6%)
Treatment	
Radiotherapy only	96 (23.18%)
CCRT	318 (76.82%)
Surgery	
Yes	212 (51.21%)
No	202 (48.79%)
Hypertension	
Yes	62 (14.97%)
No	352 (85.03%)
Diabetes mellitus	
Yes	65 (15.70%)
No	349 (84.30%)
ARE (grade)	
0	144 (34.78%)
1	250 (60.39%)
2	20 (4.83%)
3	0 (0.00%)
4	0 (0.00%)
CRE (grade)	
0	360 (86.96%)
1	47 (11.35%)
2	7 (1.69%)
3	0 (0.00%)
4	0 (0.00%)

ARE, acute radiation enteritis; BMI, body mass index; CCRT, concurrent chemoradiotherapy; CRE, chronic radiation enteritis; FIGO, International Federation of Gynecology and Obstetrics.

Table 2. Univariate analysis of predisposing factors associated with ARE in cervical cancer patients.

Characteristics	n	Grade					p
		0	1	2	3	4	
Age (years)							0.066
≥60	122	57	54	11	0	0	
<60	292	87	196	9	0	0	
BMI (kg/m^2)							0.983
>24	174	61	104	9	0	0	
≤24	240	83	146	11	0	0	
Surgery							<0.001
No	202	122	76	4	0	0	
Yes	212	22	174	16	0	0	
Treatment							0.85
CCRT	318	112	190	13	0	0	
Radiotherapy only	96	32	60	4	0	0	
Diabetes mellitus							<0.001
Yes	65	11	40	14	0	0	
No	349	133	210	6	0	0	
FBG (mmol/L)							<0.001
≥6.1	119	30	74	15	0	0	
<6.1	295	114	176	5	0	0	
Hypertension							<0.001
Yes	62	3	43	16	0	0	
No	352	141	207	4	0	0	
Radiation dose (Gy)							<0.001
≥56	101	23	65	13	0	0	
<56	313	121	185	7	0	0	

BMI, body mass index; CCRT, concurrent chemoradiotherapy; FBG, fasting blood glucose.

or chemoradiotherapy. Of the patients receiving radiotherapy (including external-beam radiotherapy and brachytherapy), 96 patients were treated with radiotherapy alone, and 318 patients received concurrent chemoradiotherapy. Notably, ARE was observed in 270 (65.2%) of the 414 patients, of whom 250 (60.4%) and 20 (4.8%) had grade 1 and grade 2, respectively. CRE occurred in 54 (13.1%) of the 414 patients, of whom 47 (11.4%) and 7 (1.7%) had grade 1 and grade 2, respectively. No patient experienced grade 3/4 ARE or CRE.

To investigate the predisposing factors for ARE, we first conducted a univariate analysis (summarized in Table 2). Of the variables of interest, we found that no prior surgery, radiation dose over 56 Gy, hypertension, diabetes mellitus, and hyperglycemia were significantly correlated with ARE in patients with cervical cancer. A multivariate analysis confirmed that no prior surgery (95% CI –3.240 to –2.129, $p < 0.001$), radiation dose over 56 Gy (95% CI –2.080 to –0.991, $p < 0.001$), hypertension (95% CI –3.447 to –1.530, $p < 0.001$), and hyperglycemia (95% CI –1.319 to –0.225, $p = 0.006$), were independent predisposing factors for ARE patients with in cervical cancer (Table 3).

Next, we performed a univariate analysis to evaluate the predisposing factors associated with CRE in patients with cervical cancer (summarized in Table 4). The univariate analysis revealed that no prior surgery, hypertension, diabetes mellitus, and hyperglycemia were significantly correlated with CRE. In addition, hypertension (95% CI –1.831 to –0.250, $p = 0.01$), diabetes mellitus (95% CI –1.802 to –0.216, $p = 0.01$), and hyperglycemia (95% CI –2.336 to –0.972, $p < 0.001$) were considered independent predisposing factors for CRE in patients with cervical cancer on multivariate analysis (Table 5).

The above-mentioned results suggest that high glucose levels as well as diabetes mellitus significantly impact the incidence of both ARE and CRE. Based on this, we evaluated the level of FBG for patients with cervical cancer and diabetes mellitus. Among the 65 patients with diabetes mellitus, 33 patients (50.8%) had good glucose control, while the other 32 (49.2%) had poor glucose control (Table 6). The incidences of ARE (90.6% vs. 75.8%, $p < 0.001$) and CRE (62.5% vs. 21.2%,

Table 3. Multivariate analysis of predisposing factors associated with ARE in cervical cancer patients.

Characteristics	95% CI	*p*
Surgery	−3.240 to −2.129	<0.001
Radiation dose	−2.080 to −0.991	<0.001
FBG	−1.319 to −0.225	0.006
Diabetes mellitus	−0.420 to 1.125	0.308
Hypertension	−3.447 to −1.530	<0.001

FBG, fasting blood glucose.

$p = 0.001$) were significantly higher in patients with diabetes mellitus and poor glucose control than in patients with good glucose control.

4. Discussion

With improvements in quality of life, radiation-induced toxicity is gaining increased attention as an important health issue. Both treatment- and patient-related factors are expected to contribute to the development of RE; however, the specific pathogenesis of RE is not fully understood. The currently understood mechanisms are as follows: (1) direct radiation damage to the intestinal mucosa leads to diarrhea by the disruption of absorption/secretion and increased intestinal permeability; (2) vascular injuries caused by radiation promote endothelial swelling, crypt epithelial cell loss, and reduced mucosal blood flow, resulting in impaired intestinal barrier function [12, 13]; (3) the gut microbiome might play a role in the initiation and progression of RE; thus, alteration of the intestinal flora may contribute to RE [14]; and (4) radiation can trigger the release of various inflammatory cytokines, and the imbalance between proinflammatory and anti-inflammatory cytokines accelerates chronic fibrosis [15, 16].

In the current study, ARE occurred in 65.2% of all enrolled patients, while 13.1% of patients had CRE, which was consistent with the incidence of RE reported in previous literature [17]. Notably, no grade 3/4 RE was observed in this study, which may be owing to the application of IMRT, which greatly spares normal tissues. Chen *et al.* [18] evaluated toxicity and clinical outcomes in patients with advanced cervical cancer after hysterectomy receiving either four-field radiotherapy or IMRT. They reported that IMRT as an adjuvant treatment significantly reduced acute gastrointestinal toxicity compared to conventional radiation therapy, which could be the result of fewer doses to the small intestine [18]. Here, we retrospectively analyzed the correlations between RE and the clinical characteristics of patients with cervical cancer undergoing radiotherapy. The results showed that the potential predisposing factors for ARE included no prior surgery, total radiation dose, hypertension, and hyperglycemia; additionally, hypertension, diabetes mellitus, and hyperglycemia were predisposing factors for CRE. Other patient-related factors were statistically insignificant, including age, BMI and concurrent chemotherapy.

Table 4. Univariate analysis of predisposing factors associated with CRE in cervical cancer patients.

Characteristics	n	Grade					*p*
		0	1	2	3	4	
Age (years)							0.104
≥60	122	101	18	3	0	0	
<60	292	259	29	4	0	0	
BMI (kg/m^2)							0.557
>24	174	147	26	2	0	0	
≤24	240	213	21	5	0	0	
Surgery							<0.001
No	202	189	11	2	0	0	
Yes	212	171	36	5	0	0	
Treatment							0.739
CCRT	318	276	36	6	0	0	
Radiotherapy only	96	84	11	1	0	0	
Diabetes mellitus							<0.001
Yes	65	38	21	6	0	0	
No	349	326	26	61	0	0	
FBG (mmol/L)							<0.001
≥6.1	119	82	30	7	0	0	
<6.1	295	278	17	0	0	0	
Hypertension							<0.001
Yes	62	36	22	4	0	0	
No	352	324	25	3	0	0	
Radiation dose (Gy)							0.09
≥56	101	82	14	5	0	0	
<56	313	278	33	2	0	0	

BMI, body mass index; CCRT, concurrent chemoradiotherapy; FBG, fasting blood glucose.

Numerous studies have shown that the total dose of radiation delivered is a major risk factor for RE [19]. On univariate analysis, a radiation dose over 56 Gy was significantly associated with an increased incidence of ARE and CRE ($p < 0.001$). Besides, the total radiation dose was considered an independent risk factor for ARE in patients with cervical cancer. Kavanagh *et al.* [20] estimated that doses starting from 50 Gy for partial irradiation and 40 Gy for whole irradiation of the intestines showed a 50% risk for intestinal toxicities at 5 years. Li *et al.* [21] assessed the correlation between the volume of irradiated small bowel and the development of acute diarrhea in patients with gynecologic cancer. They found that the irradiated small bowel volume was an independent risk factor for acute radiation-induced intestinal toxicities. Additionally, Chen *et al.* [22] showed that the maximum radiation dose to the small bowel loops was correlated with chronic gastrointestinal complications, and the optimal threshold was less than 56 Gy. Thus, to minimize severe acute radiation-induced toxicities, the volume of the intestines receiving over 45 Gy is proposed to be less than 195 cc [20].

It has been previously demonstrated that a history of abdominal surgery is associated with a higher risk of RE, especially CRE [23]. Huang *et al.* [24] have shown that prior

Table 5. Multivariate analysis of predisposing factors associated with CRE in cervical cancer patients.

Chracteristics	95% CI	*p*
Surgery	−1.492 to 0.035	0.062
Radiation dose	−1.298 to 0.119	0.103
FBG	−2.336 to −0.972	<0.001
Diabetes mellitus	−1.802 to −0.216	0.013
Hypertension	−1.861 to −0.250	0.01

CRE, chronic radiation enteritis.

Table 6. Effect of glucose control on ARE and CRE in cervical cancer patients with diabetes mellitus.

Characteristics	n	Grade					*p*
		0	1	2	3	4	
ARE							<0.001
Good glucose control	33	8	24	1	0	0	
Poor glucose control	32	3	16	13	0	0	
CRE							0.001
Good glucose control	33	26	6	1	0	0	
Poor glucose control	32	12	15	5	0	0	

ARE, acute radiation enteritis; CRE, chronic radiation enteritis.

abdominal surgery could increase the possibility of higher-grade intestinal toxicities, which was related to a larger volume of small bowel irradiation. In contrast with previous reports, we found that patients who did not undergo prior surgery had significantly higher incidences of ARE and CRE than patients who did. The discrepancy might be due to the different radiation doses and methods. Patients with cervical cancer receive adjuvant radiotherapy following hysterectomy, whereas inoperable patients receive definitive radiotherapy, which could result in a higher radiation dose to the parametrium.

A growing body of evidence has shown that diabetes mellitus as well as the evaluated FBG level are associated with poor responses to treatment and regarded as independent prognostic factors for patients with cervical cancer [25, 26]. In the present study, we found that both diabetes mellitus and hyperglycemia significantly correlated with increased incidences of ARE and CRE ($p < 0.001$). Furthermore, we found that patients with diabetes mellitus and poor glucose control were more likely to experience acute and chronic intestinal complications when receiving radiotherapy, which was confirmed by another study [27]. Interestingly, regardless of diabetes mellitus status, an elevated FBG level also plays an important role in radiation-induced intestinal toxicities. Generally, hyperglycemic conditions can induce the production of reactive oxygen species which aggravate intestinal epithelial injuries [28]. Moreover, inflammatory responses can be accelerated by hyperglycemia, thus affecting the self-repair of damaged epithelial cells [29]. Thus, the control of blood glucose may be of clinical significance for reducing the occurrence of RE in patients with cervical cancer.

Comorbidities such as hypertension play a role in microvascular dysfunction, which predisposes patients to increased vascular damage induced by radiotherapy [19]. To date, the role of hypertension as an independent risk factor for RE remains unclear. Some research has demonstrated a significant correlation between hypertension and RE, while others have shown the opposite [30]. Interestingly, some studies have suggested that hypertension may be protective against the development of chronic complications, as antihypertensive drugs can help reduce radiation-induced toxicity [31]. In our study however, we showed that hypertension was significantly associated with the occurrence of RE, serving as an independent risk factor for ARE and CRE.

There were several limitations of our study. The follow-up duration was only 14 months in this study, which might be insufficient to evaluate the long-term side effects of radiotherapy. Moreover, this was a single-center, retrospective study with a small sample size. Therefore, large prospective studies are needed to further confirm our results.

In conclusion, we retrospectively evaluated the clinical characteristics associated with the risk of developing RE in patients with cervical cancer undergoing radiotherapy. Apart from treatment-related factors such as the radiotherapy method and total radiation dose, comorbidities including diabetes mellitus, hyperglycemia, and hypertension should be considered independent predisposing factors for RE. Therefore, the positive control of blood pressure and glucose level before and during radiotherapy is of clinical significance. Further investigation is warranted to confirm these effects on the development of radiation-induced intestinal toxicities.

Abbreviations

ARE, acute radiation enteritis; CCRT, concurrent chemoradiotherapy; CRE, chronic radiation enteritis; CTV, clinical target volume; FBG, fasting blood glucose; IMRT, intensity-modulated radiation therapy; PTV, planning target volume; RE, radiation enteritis.

Author contributions

JF—data collection, project development, and manuscript drafting; JMF—data collection and analysis; ALW—data analysis and methodology; YFZ—conceptualization, manuscript editing, and supervision; YL—conceptualization, project development, data analysis, manuscript editing, and supervision.

Ethics approval and consent to participate

The Ethics Committee of Anhui Provincial Cancer Hospital approved the study (No. 2021–FLK–02). The requirement for informed consent was waived due to the retrospective nature of this study.

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Conflict of interest

The authors declare no conflict of interest.

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