Severe Late Complications in Patients with Uterine Cancer Treated with Postoperative Radiotherapy

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Abstract. *Aim: Severe late complications, particularly radiation enterocolitis and leg edema, remain major problems in patients with uterine cancer, who have undergone hysterectomy and postoperative external beam radiotherapy (EBRT). We carried out this retrospective analysis to identify the incidence of risk factors for such complications. Patients and Methods: The records of 228 patients, who underwent radical hysterectomy and postoperative EBRT (uterine cervix: 149 patients; uterine corpus: 79 patients) were reviewed retrospectively. The majority of the patients (90.8%) were treated with 50 to 50.4 Gy EBRT in conventional fractionations with anteroposterior fields. Intracavitary brachytherapy (ICBT) was administered to 9 patients (3.9%), and 35 patients (15.2%) received chemotherapy. The median follow-up for all 228 patients was 81.7 months (range, 1-273 months). Results: Nineteen patients (8.3%) developed severe radiation enterocolitis with a median latency of 12.6 months, and the ileum was the most frequently affected site. On multivariate analysis, smoking was an independent predictor of severe radiation enterocolitis. Nineteen patients (8.3%) developed severe leg edema with a median latency of 32.7 months. The degree of leg edema did not improve in any of the 19 patients despite intensive treatment. On multivariate analysis, addition of ICBT was an independent predictor of severe leg edema. Conclusion: Severe radiation enterocolitis and severe leg edema were each observed in approximately 8% of patients with uterine cancer, who underwent postoperative radiotherapy. Severe radiation enterocolitis correlated strongly with smoking, and severe leg edema correlated strongly with addition of ICBT. These factors should be considered before administering postoperative radiotherapy to uterine cancer patients.*

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Surgery continues to play a very important role for patients with uterine cancer. In patients with uterine corpus cancer, surgery is considered to be the standard treatment for both early-stage and advanced-stage tumors, as well as for recurrent tumors (1). In patients with early-stage uterine cervical cancer, surgery has also been accepted as a preferred treatment (2).

However, various risk factors, such as pelvic lymph node metastasis, bulky tumor size, deep stromal invasion, and positive resection margins, have been shown to correlate with an increased incidence of treatment failure in patients with uterine cancer (3, 4). Adjuvant treatment, including postoperative radiotherapy, is usually recommended for patients with these risk factors, and several studies have shown that adjuvant radiotherapy significantly reduces the rate of local recurrence in this patient population (4-6). Although the role of postoperative radiotherapy has not been defined clearly, several additional reports have found that for high-risk patients, postoperative radiotherapy significantly improves relapse-free survival and marginally increases overall survival (4). Therefore, postoperative adjuvant radiotherapy appears to benefit certain subsets of patients with these tumors.

Dispite improved methodology and the availability of better equipment for radiotherapy, severe late complications, particularly radiation enterocolitis and leg edema, have remained major problems in patients, who have undergone radical hysterectomy and postoperative pelvic radiotherapy (7-10). The incidence of radiation enterocolitis varies from 5% to 15% in patients treated with pelvic radiotherapy (11-13). Of these, some patients with chronic radiation enterocolitis require further surgery during follow-up. Bowel

injuries that result in fistula, stricture and chronic malabsorption are potentially life-threatening and impact patients' quality of life (QOL) (14). Leg edema is a serious late complication of postoperative radiotherapy that can cause severe leg ulcers and deteriorate QOL. Thus, it is important to reduce the incidences of severe late gastrointestinal complications and severe leg edema when administering pelvic radiotherapy for uterine cervical and uterine corpus cancer. However, information regarding the risk factors for severe radiation enterocolitis and severe leg edema in patients who undergo surgery and postoperative radiotherapy is limited.

In the current study, we retrospectively analyzed the clinical data of 228 patients with uterine cancer who were treated with surgery and pelvic radiotherapy, to identify the incidence, the risk factors and clinical outcomes of severe radiation enterocolitis and severe leg edema in this patient population.

Patients and Methods

Patients. Between 1984 and 2004, 1266 patients with uterine cancer were treated at the University of the Ryukyus Hospital, and of these, 231 patients underwent surgery and postoperative radiotherapy. Three patients had a histological diagnosis of sarcoma: the remaining 228 patients, who had a histological diagnosis of carcinoma were the subjects of this study. This study followed the principles of the Declaration of Helsinki (15), and informed consent was obtained from all 228 patients. Surgery was predominantly radical hysterectomy for uterine cervical cancer and total abdominal hysterectomy for uterine corpus cancer. Pelvic lymphadenectomy was defined as dissection of the lymph nodes around the common, external and internal iliac vessels and of the nodes located in the deep obturator fossa. The median age of all 228 patients was 51 years (range, 23-80 years). All patients underwent a primary medical evaluation, including a detailed history, a review of symptoms, and a physical examination, before a treatment plan was formulated, and follow-up information was obtained from the patients' records or from communications with patients and/or their physicians. We analyzed each patient's tobacco exposure, but we could not quantify the amount of tobacco smoking due to the limited information available and the retrospective nature of the analysis.

Treatment. Radical hysterectomy was performed in 166 patients (141 of 149 patients with uterine cervical cancer and 25 of 79 patients with uterine corpus cancer), and the remaining 62 patients underwent total abdominal hysterectomy. In patients who underwent radical hysterectomy, pelvic lymph node resections were performed; however, we could not investigate the number of lymph nodes dissected due to the limited information available. Detailed methods of pelvic external beam radiotherapy (EBRT) conducted at our institution have been described previously (16, 17). In brief, most of the patients underwent pelvic radiotherapy 5 days per week with daily fractions of 1.8 to 2 Gy. Pelvic radiotherapy was delivered primarily using anterior and posterior opposed fields; 4 patients (2%) were treated with four fields. The upper border of the radiation field was at the L4/5 interspace when whole pelvic irradiation was used. EBRT was delivered with a 15 or 18 MV linear accelerator. The median external beam radiation dose to the pelvis was 50.4 Gy (range, 10.8-50.4 Gy), and the majority of patients (90.8%) were treated with a total dose of 50 or 50.4 Gy to the pelvis in conventional fractionations. Twenty-six patients (11.4%) received treatment to the para-aortic nodes (L1/2 interspace in the upper border) in addition to the pelvic field (extended field), and the doses to the para-aortic nodes was 45 Gy. The extended field was supplemented because of positive lymph nodes at the common iliac and/or para-aortic lesions in these 26 patients.

Nine patients (3.9%) were treated with Ir-192 high-dose rate intracavitary brachytherapy (ICBT) after EBRT. In these 9 patients, ICBT was supplemented because a positive surgical margin was identified. Detailed methods of ICBT have been described previously (18). In brief, ICBT was performed once a week with a daily dose of 6 Gy at a 0.5 cm depth up to total doses of 6-30 Gy (median, 18 Gy). Midline block into the center of the pelvic field was not used before or during ICBT.

Overall, 35 out of 228 (15.3%) patients received intravenous or intra-arterial chemotherapy as described previously (16, 17). Cisplatin was the most frequently used drug, and the main combination regimens used were fluorouracil with tegafur/uracil for uterine cervical cancer and carboplatin and adriamycin for uterine corpus cancer.

Statistical analysis. The median follow-up for all 228 patients was 81.7 months (range, 1-273 months). Late gastrointestinal complications were graded in accordance with the Radiation Therapy Oncology Group (RTOG) criteria for bowel complications (19), and the Late Effects in Normal Tissues Subjective, Objective, Management, and Analytic (LENT SOMA) score was used to grade severe leg edema and cystitis (20). In the current study, severe radiation enterocolitis was defined as the clinical condition of requiring medical intervention, such as decompression or surgery (RTOG grade 3). Severe leg edema was defined as the clinical situation in which secondary or total dysfunction occurred and required medical intervention (LENT SOMA grade 3). Severe cystitis was defined as ulceration into muscle (LENT SOMA grade 3). We defined patients as smokers when smoking was documented in their medical records. The chi-square test and multiple stepwise logistic regression analysis were used to evaluate the relationship between variables and the occurrence of severe radiation enterocolitis and severe leg edema. The distribution between observed and expected rates was compared with a Hosmer–Lemeshow test (21). Overall and cancer-specific survival rates were calculated actuarially with the Kaplan-Meier method (22) and were measured from the day of surgical resection. A probability level of 0.05 was chosen for statistical significance. Statistical analysis was performed with the SPSS software package (version 13.0; SPSS, Inc., Chicago, IL, USA).

Results

The development of severe radiation enterocolitis, severe leg edema, and cystitis was analyzed in 228 patients. Of these 228 patients, 19 patients (8.3%) developed severe radiation enterocolitis requiring surgical management, and 19 patients (8.3%) developed severe leg edema with secondary dysfunction. Three patients developed both severe radiation enterocolitis and severe leg edema. One patient (0.4%) developed late severe cystitis requiring surgical treatment. No other severe complications were observed in the present study.

Table I. *The patient and the treatment characteristics for severe enterocolitis and severe leg edema in patients with uterine cancer treated with external beam radiotherapy.*

	No. of patients (n=228)	No. of patients with severe enterocolitis (%) (n=19)	*p*-Value	No. of patients with severe leg edema (%) (n=19)	*p*-Value
Tumor stage (FIGO)			0.302		0.483
I, II	197	15 (8)		18 (9)	
III, IV	31	4 (13)		1 (3)	
Age (years)			0.947		0.947
>65	26	2 (8)		2 (8)	
<65	202	17 (8)		17 (8)	
Body mass index			0.09		1.000
<22	89	11 (12)		7 (8)	
>22	139	8 (6)		12 (9)	
Smoking			0.017		0.745
es	36	7 (19)		2 (6)	
No	192	12 (6)		17 (9)	
DM			0.640		0.373
Yes	17	2 (12)		0 (0)	
No	211	17 (8)		19 (9)	
Hypertension			0.601		0.159
Yes	68	7 (10)		2 (3)	
No	160	12 (7)		14 (8)	
Alcohol drinking			1.000		0.067
Yes	12	1 (8)		3 (25)	
No	216	18 (8)		16 (7)	
Hyperlipidemia			0.703		0.703
Yes	22	1 (5)		1 (5)	
No	206	18 (9)		18 (9)	
Histological type			0.815		0.149
SCC	115	9 (8)		6 (5)	
not SCC	113	10 (9)		13 (12)	
Total dose (Gy)			0.703		0.663
>50	209	17 (8)		17 (8)	
<50	19	2 (11)		2 (10)	
Treatment field			0.246		1.000
Extended field	26	4 (15)		2 (8)	
Whole pelvis	202	15 (7)		17 (8)	
ICBT			0.550		0.003
Yes	9	1 (11)		4 (44)	
No	219	18 (8)		15 (7)	
Chemotherapy			0.183		0.504
Yes	35	5 (14)		4 (11)	
No	193	14 (7)		15 (8)	
Interval between two treatments*			0.888		0.888
<6 weeks	172	15 (9)		15 (9)	
>6 weeks	56	4 (7)		4 (7)	
Surgical treatment			0.175		0.109
Radical hysterectomy	166	11 (7)		17 (10)	
Total abdominal hysterectomy	62	8 (13)		2 (3)	

FIGO: International Federation of Gynecology and Obsterics; DM: diabetes mellitus; SCC: squamous cell carcinoma; ICBT: intracavitary brachytherapy; *interval between the day of surgery and the day of postoperative radiotherapy.

The characteristics of the patients who developed severe radiation enterocolitis are listed in Table I. Sites of radiation enterocolitis included the ileum (n=16), the ascending colon (n=3) and both the ileum and ascending colon (n=2). The median latency of severe radiation enterocolitis after postoperative EBRT for all 19 patients was 12.6 months (range, 2.8-129.1 months). The median external beam radiation dose to the pelvis for all 19 patients was 50.4 Gy (range, 18-50.4 Gy), and 1 patient received only 18 Gy EBRT because radiation enterocolitis occurred during radiotherapy.

For treatment of radiation enterocolitis, only 1 patient underwent intestinal decompression alone, while the remaining 18 patients underwent intestinal resection in addition to intestinal decompression. Only 1 out of these 18 patients who underwent intestinal resection in addition to intestinal decompression experienced intestinal dysfunction after treatment for radiation enterocolitis.

At the time of the analysis, 1 patient had died from radiation enterocolitis, and 5 patients had died from primary cancer. The 5-year actuarial overall survival rate from the day of occurrence of severe enterocolitis for all 19 patients was 71.1 %.

Tables I and II show the results of univariate and multivariate analyses of potential risk factors for the occurrence of severe radiation enterocolitis. Smoking had a significant impact on severe radiation enterocolitis on univariate analysis (p=0.003), and on multivariate analysis (p=0.013). The p-value of the Hosmer–Lemeshow test was 0.271, which means the observed and expected event rates could be considered equal.

The characteristics of the patients who developed severe leg edema are listed in Tables I and II. In 16 out of 19 patients (81%), postoperative radiotherapy was initiated within 6 weeks after surgery for uterine cancer. The median latency of severe leg edema for all 19 patients after postoperative radiotherapy was 29.7 months (range 0.8–205.0 months). Of these 19 patients, 17 patients (89%) required hospitalization. Intensive treatments for severe leg edema, such as compression therapy, elastic stockings, diuretic agents, antibiotics and bed rest with lower limb elevation, were provided for all 19 patients. For 3 patients, surgical intervention, such as venous-lymphatic anastomosis, was administered. However, the degree of leg edema did not change in any of the 19 patients despite these interventions.

At the time of this analysis, no patient with severe leg edema had died from uterine cancer, and the 5-year actuarial overall survival rate from the day of occurrence of severe leg edema for all 19 patients was 89.5%.

Tables I and II show the results of univariate and multivariate analyses of risk factors for the occurrence of leg edema. Addition of ICBT had a significant impact on leg edema on univariate analysis (p=0.003), and on multivariate analysis (p=0.001). The p-value of the Hosmer–Lemeshow test was 0.985, which means the observed and expected event rates could be considered equal.

Severe cystitis was observed in 1 patient, and she suffered a bladder-intestinal fistula. However, because of the limited information available, the exact reasons for this could not be determined from the medical records.

Table II. *Multivariate analysis of various potential prognostic factors for enterocolitis and leg edema in patients with uterine cancer treated with external beam radiotherapy.*

	p-Value	OR (95% CI)
Severe enterocolitis		
Smoking	0.013	3.623 (1.318-10.000)
Severe leg edema		
ICBT	0.001	10.870 (2.639-45.454)

DM: Diabetes mellitus; RR: relative risk; OR: odds ratio; CI: confidence interval; ICBT: intracavitary brachytherapy.

Discussion

In the current study, 8.3% (19/228) of patients with uterine cancer who underwent radiotherapy with a median total dose of 50 Gy EBRT developed severe radiation enterocolitis requiring surgery. Previous reports have also indicated that approximately 3-9% of patients developed radiation enterocolitis requiring surgery when total doses of 45-55 Gy EBRT with conventional fractionations were used (7, 23, 24). These results are consistent with the reported tolerance of the small bowel and colon of 50-55 Gy with conventional fractionation, which is associated with an approximately 5% risk of radiation-induced small bowel stricture, perforation, and hemorrhage (25, 26). Table III summarizes the results of previous reports showing the frequency of severe radiation enterocolitis for patients with uterine cancer who underwent postoperative radiotherapy (27-30). Although the treatment methods differed, the overall frequency of severe enterocolitis after postoperative EBRT was 5.7-10.0%. These results suggest that severe radiation enterocolitis will develop in approximately 5-10% of patients with uterine cancer who undergo postoperative radiotherapy.

Concerning the site of radiation enterocolitis, our results indicated that the ileum was the most frequently affected site. Several other reports have also indicated that the ileum is the most frequently affected site (24, 31, 32). A possible explanation for the high incidence of radiation enterocolitis in the ileum may be that pelvic radiotherapy primarily involves the ileum, and that the ileum is relatively radiosensitive compared to other regions of the intestine (24). Several lines of evidence also suggest that such post-irradiation complications are attributable to capillary damage, microvascular occlusion, and increased fibrosis (33, 34).

The current study, also, indicated that smoking was a significant risk factor for the development of severe radiation enterocolitis after postoperative radiotherapy. Although the effects of smoking on the late effects of subdiaphragmatic irradiation have not been well analyzed in detail, several studies have suggested that persistent smokers have a higher risk of radiation-related complications, possibly due to a direct irritant effect or vascular toxicity effects (35-37). Eifel *et al*. demonstrated that smoking had a profound influence on the incidence of small bowel complications in patients with cervical cancer (37). Kucera *et al*. also found a significant

Table III. *Summary of previous reports concerning severe radiation enterocolitis (postoperative radiotherapy cases).*

Author (ref)	No. of cases	Primary site	Severe enterocolitis*	EBRT (Gy)	Extended field	ICBT	Chemotherapy
Fiorica *et al*. (27)	50	Cervix	5 (10%)	47 (average)	Y	Y	N
Grigsby (28)	140	Cervix	8 (5.7%)	50.4 (mean)	N	Y	N
Okuma *et al*. (29)	111	Corpus	9 (8.1%)	50-50.4	Y	N	Y
Greven *et al*. (30)	44	Corpus	4 (9.1%)	45	NA	Y	Y
Current study	229	Cervix & corpus	19 (8.3%)	50 (median)	Y	Y	Y

EBRT: External beam radiotherapy; ICBT: intracavitary brachytherapy (high-dose rate); NA: not available; Y: yes (done); N: no (not done). *Severe enterocolitis is defined as symptoms that required frequent medication or surgical intervention.

Table IV. *Summary of previous reports concerning severe leg edema (postoperative radiotherapy cases).*

Author (ref)	No. of cases	Primary site	Severe leg edema*	EBRT (Gy)	Extended field	ICBT	Chemotherapy
Grigsby *et al*. (28)	140	Cervix	8 (5.7%)	50.4 (mean)	N	Y	N
Hart *et al*. (43)	55	Cervix	1 (1.8%)	45-50	NA	Ya	N
Landoni *et al*. (44)	108	Cervix	10 (9.3%)	50.4	Y	Yb	N
Current study	229	Cervix & corpus	19 (8.3%)	50 (median)	Y	Y	Y

EBRT: External beam radiotherapy; ICBT: intracavitary brachytherapy (high-dose rate); NA: not available; Y: yes (done); N: no (not done); a: low-dose rate ICBT was performed for some of their patients; b: low-dose rate ICBT was performed for all patients. *Severe leg edema is defined as symptoms that required frequent medication or surgical intervention.

correlation between smoking and the overall rate of major complications in patients with uterine cervical cancer (36). In the current study, the incidence of radiation enterocolitis was significantly higher in patients who smoked than in nonsmokers, and on multivariate analysis, smoking was identified as an independent risk factor. These results indicate that smoking is a significant risk factor for severe radiation enterocolitis after surgery and postoperative radiotherapy. Therefore, more careful dose prescription for the intestine would be required for smokers.

Optimal management of patients with severe radiation enterocolitis remains controversial. Although several authors have advocated the use of bypass procedures (13, 31), recent reports have suggested that small bowel injury should be treated by liberal resection of the affected bowel followed by careful anastomosis of the disease-free ends (8, 9, 38). Regimbeau *et al*. compared the postoperative mortality, early and late morbidity, and long-term survival after intestinal resection or conservative surgical management in 149 patients with gynecologic, digestive and other types of cancer (8). They found that intestinal resection provided a smaller re-operation rate and a better 5-year survival rate compared to conservative treatment. Shiraishi *et al*. also found that intestinal resection in addition to decompression reduced the risk of death compared to intestinal decompression alone in 54 patients with uterine cervical, uterine corpus and other gynecological cancer (9). In the current study, 18 out of 19 patients who developed radiation enterocolitis were treated with surgical resection in addition to decompression, and only 1 of the 18 patients suffered intestinal dysfunction following surgical resection. These results suggest that generous resection of the affected bowel appears to be the preferred therapy for severe radiation enterocolitis in this patient population.

To reduce the risk of late severe gastrointestinal complications, several therapeutic approaches have been suggested. Visualization of the small bowel by oral contrast during treatment planning for pelvic irradiation has been associated with a reduction in the incidence and duration of small bowel morbidity (39). Prone treatment on a belly-board has been reported to reduce the volume of small bowel irradiated significantly in women receiving adjuvant radiotherapy for gynecologic cancer (40). Because the use of anterior/posterior fields is associated with higher dose inhomogeneity in the pelvis, intensity-modulated radiotherapy (IMRT) has emerged as an attractive strategy that allows the production of concave dose distributions, and therefore potentially reduces the radiation dose to radiosensitive organs within the pelvic cavity (41, 42). Further studies are required to develop more sophisticated methods to reduce the total dose to the intestines, especially to the ileum.

In the current study, severe leg edema developed in 8.3% (19/228) of the patients with uterine cancer who underwent postoperative radiotherapy, with a median latency of 29.7

months. Several authors have also reported the frequency of severe leg edema in patients with uterine cancer treated with postoperative radiotherapy (Table IV). These results, together with our results, indicate that severe leg edema occurs in approximately 5-10% of patients treated with postoperative radiotherapy.

The risk factors for severe leg edema in patients who undergo postoperative radiotherapy have not been well documented. Our results indicate that addition of ICBT was an independent risk factor for severe leg edema in patients who undergo postoperative EBRT. A possible reason for severe leg edema may be that the addition of ICBT after EBRT may cause more intense disruption of capillary and lymphatic systems, microvascular occlusion and increased fibrosis compared to EBRT alone. Furthermore, in the current study, intensive treatments for severe leg edema were not effective in improving the degree of leg edema in any of the 19 patients. Therefore, severe leg edema appears to be very difficult to treat and reduces the QOL of these patients. Therefore, careful application of ICBT may be considered when combining it with EBRT for patients with uterine cancer. However, ICBT delivers the dose to a small volume of vaginal mucosa to a depth of 0.5 cm, and doses to pelvic lymphatics may not be very high. Further studies are required to investigate the influence of ICBT on the pelvic regions.

Concerning the durations between the day of surgery and the beginning of radiotherapy, Grigsby found that the incidence of leg edema was significantly higher if postoperative irradiation was begun within 6 weeks after surgery compared to more than 6 weeks after surgery (28). In the current study, in 16 out of the 19 patients (84.2%) who developed severe leg edema, postoperative radiotherapy was initiated within 6 weeks after surgery. Therefore, it may be preferable to begin postoperative radiotherapy more than 6 weeks after surgery to reduce the incidence of severe leg edema. However, the interval between the day of surgery and the beginning of radiotherapy had no significant relationship with severe leg edema in this study. Further studies are required to evaluate optimal treatment schedules, particularly with respect to the timing of postoperative radiotherapy after surgery.

In conclusion, our results indicate that severe enterocolitis and severe leg edema each occurred in approximately 8% of patients with uterine cancer who underwent surgery and postoperative radiotherapy. Our results also indicate that severe radiation enterocolitis frequently occurred at the terminal ileum and was strongly correlated with smoking. Severe leg edema is very difficult to treat in this patient population, and it may be correlated with the addition of ICBT. These factors should be considered before administering postoperative radiotherapy to patients with uterine cancer. However, the current study was a retrospective study of various treatment modalities, and further prospective studies are required to confirm our results.

Conflict of Interest

There is no conflict of interest regarding the manuscript.

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