Early Bowel Complications Following Radiotherapy of Uterine Cervix Carcinoma

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Purpose : This study evaluated early bowel complications in cervix cancer patients, following external radiotherapy (ERT) and high dose rate intracavitary radiation (HDR ICR). Factors affecting the risk of developing early bowel complications and its incidence are analyzed and discussed

Materials and Methods : The study is the retrospective review of 66 patients who received radiotherapy at Chungbuk National University Hospital from April 1994 to December 1998. The patients underwent 41.4 or 50.4 Gy ERT according to FIGO stage and tumor size, then A point dose was boosted to 71.4 or 74.4 Gy using a remotely controlled afterloading Buchler HDR ICR. The EORTC/RTOG morbidity criteria were used to grade early bowel complications, which are valid from day 1, the commencement of therapy, through day 90. The actua rial incidence, severity of complications were investigated and clinical pretreatment factors relevant to complications were found through univariate (Wilcoxon) and multivariate (Cox proportional hazard model) analysis.

Results : Of the 66 patients, 30 pat ients (46%) developed early bowel complications; 25 patients (38%) with grade 1 or 2, 4 patients (6%) with grade 3 and 1 patient (2%) with grade 4. The complications usually began to occur 3 weeks after the commencement of radiotherapy. The actuarial incid ence of early bowel complications was 41% at 10 weeks. The early bowel complications were associated significantly with an old age and a history of previous abdomino-pelvic surgery. All three patients who had a protracted overall treatment time (about 2 we eks) due to severe bowel complication, suffered from pelvic recurrences.

Conclusion : Forty six percent of patients experienced early bowel complications, most of which were grade 1 or 2 and relieved spontaneously or by medication. The patients with an old age or a previous surgery have a high probability of early complications and they may be less compliant with planned radiotherapy. So more careful precaution is necessary for these patients.

Key Words : Early bowel complications, Radiotherapy, Cervix cancer

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INTRODUCTION

The results of radiotherapy of the uterine cervix carcinoma have been markedly improved with arena of megavoltage external radiotherapy and intracavitary radiation. But still about 30 40% of patients with even early stage disease will suffer from recurrences depending on the tumor size and lymph node involvement.[1] This result suggests that higher dose is necessary to increase the cure rate. But major obstacle to this improvement is the occurrence of complications especially in the lower gastrointestinal tract. There are two kinds of bowel complications, early and late.[2] The late complication is sometimes fatal, intractable in spite of low incidence and much has been written on the late bowel complications. On the contrary early bowel complications occurred during or shortly after the treatment and is usually mild, self-limited, drug responsive. And there is a paucity of clinical data concerning the early bowel complication. However serious early complications can affect performance status of patients, and consequently make patients less compliant with radical radiotherapy, resulting protracted overall treatment time, which is detrimental to the treatment outcome. So we herein retrospectively analyzed the 66 patients with carcinoma of the uterine cervix, treated with external radiotherapy and high dose

rate intracavitary radiation, to evaluate the incidence, severity and factors influencing the development of early bowel complications.

MATERIALS AND METHODS

From April 1994 to December 1998, 72 consecutive patients with biopsy-proven invasive carcinoma of the cervix, staged according to the FIGO classification, received radical radiotherapy at Chungbuk National University Hospital. Among them, 6 patients were excluded from this study because they were treated either incompletely or partially elsewhere. The remaining 66 patients constituted the basis of this study. Most of the patients were initially evaluated with physical and pelvic exami

nation, complete blood count, chest X-ray, intravenous pyelogram, sigmoidoscopy, cystoscopy and computerized tomography as a routine pretreatment staging work-up. Our treatment scheme is shown in Table 1. All patients were given first external radiotherapy to whole pelvis with 6 MV photon beam using 4 field box technique. The upper margin of whole pelvis field was a L5-S1 junction and daily dose was 1.8 Gy with five fractions per week. A total of 41.4 Gy to the whole pelvis was delivered for the patients with small (4 cm) Ib1, IIa disease while the remaining received 50.4 Gy. If necessary, some patients had boost treatment (about 6 Gy; 2 Gy× 3) to the parametria with the central structures shielded by 4 cm wide rectangular midline block. Following external radiotherapy, all patients received high dose rate intracavitary radiation using a remotely controlled afterloading Buchler system, which was performed twice per week with 4 or 5 Gy/fraction. The applicators were a Fletcher-Suit type tandem and two ovoids. Loading of the iridium-192 into tandem and ovoids were individualized depending on the uterus geometry and tumor configuration.

The total dose at point A was 71.4 or 74.4 Gy depending on tumor size and stage. Dose to the rectum was measured by direct insertion of dosimetric diode into the rectal reference point and double-checked by calculation with isodose curve. The rectal reference point is defined at the midpoint of the ovoid sources on the frontal radiograph and at the closest point from the source on a line drawn from the middle of the ovoid sources on the lateral radiograph. All of the patients were examined every week during the treatment and monthly follow-up was done for the first three months. The EORTC/RTOG criteria for the definition of early

bowel complications were used because it provided objective criteria possible to ensure uniformity and reliability. The criteria defined early bowel complications as those occurring within 90 days from the 1st day of treatment. Table 2 shows the details of scoring scheme of early bowel complication.[3] If patients complained of even mild symptoms but persistent, medical treatment was given. For some patients who complained of persistent diarrhea or bloody mucoid discharge without improvement despite medical treatment, sigmoidoscopy and/or barium enema were performed to verify the cause of symptoms.

The characteristics of 66 patients were as follows. The age ranged from 34 to 75 years old with the median of 56 years old. By FIGO stage, 13 patients were stage Ib; 22, IIa; 24, IIb; 5, IIIb and 2 patients were stage IVa. Histologically all of 66 patients had squamous cell carcinoma.

The actuarial incidence, severity of complications were evaluated and clinical pretreatment factors were analyzed through univariate (Wilcoxon) and multivariate (Cox proportional hazard model) analysis.[4, 5] Survival rate was not calculated because of short follow-up period which was less than 3 years.

RESULTS

Table 2. Early Bowel Complication Scoring Criteria (EORTC/RTOG)

Grade 0; no change
Grade 1; increased frequency or change in quality of bowel habits not requiring medication; rectal discomfort not requiring analgesics
Grade 2; diarrhea requiring parasympatholytic drugs(e.g., diphenoxylate); mucoid discharge not necessitating sanitary pads; rectal or abdominal pain requiring analgesics
Grade 3; diarrhea requiring parenteral support; severe mucous or blood discharge; abdominal distention (flat plate radiography demonstrates distended bowel loop)
Grade 4; acute or subacute obstruction, fistula or perforation, GI bleeding requiring transfusion, abdominal pain or tenesmus requiring tube decompression or bowel diversion.

Table 1. Treatment Scheme

Stage	External RT (Gy/Fx/Wks)		ICR (A point) (Gy/Fx/Wks)	Total (Gy)
	Whole Pelvis	Parametrium		
Small Ib1, IIa (4 cm)	41.4/23/4.5		30/6/3	71.4
Large Ib2, IIa (>4 cm)	50.4/28/5.5		24/6/3	74.4
IIb-IVa	50.4/28/5.5	6/3/0.5	24/6/3	74.4 (6)

Of

the 66 patients, 30 patients (46%) experienced early bowel complications, 26 cases (87%) of which began to occur 3 weeks(rectal dose 27 Gy, TDF 42, BED 32 Gy_{10}) after the commencement of radiotherapy as shown Fig. 1. The incidence of complications is increasing with cumulated radiation doses and there is a steep rise of incidence from 3rd to 8th week of radiotherapy. The actuarial incidence of early bowel complications was 41% at 10 weeks. Grade 1, 2 and 3, 4 complications developed in 38% and 8% respectively. Twenty five (38%) patients had mild grade 1 or 2 complications, which were easily relieved by absorbents, opioid agents, bulk forming agents. Four patients (6%) experienced grade 3 complications and one patient (2%) grade 4 complication. There was no death from any complication. The four cases with grade 3 occurred at 6th and 7th week and gradually improved with supportive care of bowel rest and IV hydration. Exceptionally one patient developed small bowel obstruction (grade 4) 2 weeks after irradiation and needed hospitalization because of colicky abdominal pain. Finally,

Fig. 1. The actuarial incidence of early bowel complications.

abdominal pain subsided and obstruction was relieved by tube decompression. Table 3 shows detailed statement of 5 patients who had grade 3, 4 bowel complications. The overall treatment time was significantly protracted in 3 patients (No 1, 2, 3). The No 1 patient who took a rest for 10 days developed parametrial and lymph node recurrence 7 months after radiotherapy and the No 2, 3 patient who took a rest for 15 days also developed local recurrences 6 and 10 months after radiotherapy respectively.

Of 30 patients who developed early bowel complications, 7 patients with persistent diarrhea or bloody mucoid discharge for more than 4 weeks did not respond to the conservative management and finally underwent sigmoidoscopy and/or barium enema. But they did not show any specific abnormal findings except for "nonspecific colitis" by sigmoidoscopy.

Various pretreatment factors such as age, stage, past medical history (hypertension, diabetes, pelvic inflammatory disease), history of previous abdomino-pelvic surgery (such as appendectomy, Caesarean section, oophorectomy, tubal ligation

performed via an abdominal incision) were analyzed univariately in Table 4. The incidence of early complications correlated significantly with patients age, advanced stage, history of previous abdomino-pelvic surgery (Wilcoxon, $P<0.05$). However, in multivariate analysis using Cox proportional hazard model, stage and past medical history showed no statistical correlation. Only significant factors were an old age (60) and a positive history of surgery (Table 5). The early complications developed in 65.5% (19 patients) of 29 patients older than 60 years while 29.7% (11 patients) of 37 patients younger than 60 years. Of 8 patients who had undergone previous surgery, 75% (6 patients) developed a early complication while 41.4% (24 patients) of 58 patients who had no history of surgery ($P<0.05$). A statistical correlation of various pretreatment factors and the severity of complication was not seen because of small numbers of grade 3, 4 complications. But it seemed like external radiation dose played a role for severe complications considering the fact that all of the

grade 3, 4 complications took place after receiving 50.4 Gy whole pelvis dose (TDF 79,   BED 59 Gy_{10}) and   table 3 suggested that an old age and a history of abdomino-pelvic surgery might be correlated with grade 3, 4 complications
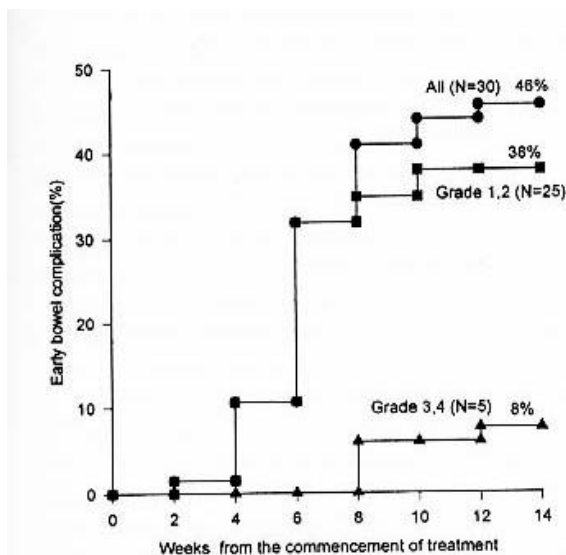
Table 3. Details on Patients with Grade 3, 4 Complications

No.	Grade	Age	Stage	Onset (from 1st day Tx)	Previous Op History	Symptoms
1	III	71	IIb	7 wks	yes	severe diarrhea parenteral support
2	III	66	IIIb	6 wks	yes	distended bowel loop in simple abdomen
3	III	61	IIa	7 wks	yes	severe diarrhea parenteral support
4	III	63	IIb	6 wks	no	distended bowel loop in simple abdomen
5	IV	69	IIIb	11 wks	yes	subacute intestinal obstruction

DISCUSSION AND CONCLUSION

Pathologically, mechanism of early bowel complication is well elucidated.[6, 7] Acute bowel injury is related to the rapid turnover of the mucosal cells. The proliferative zone of mucosal epithelium is located in crypts of Lieberkuhn and is one of the most radiosensitive tissues in the body. Within a few hours after single exposure, the mitotically active cells of the crypts show pyknosis, karyorrhexis and karyolysis. Loss of crypt cells, shortening of villi, and appearance of cystic crypt dilatation occur progressively, reaching maximum in the ensuing days. By the second through fourth weeks there may be variable infiltration of the lamina propria by inflammatory cells. Sometimes focal erosions occur. A typical change of the mucosa of the rectum is the presence of the

Table 4. Risk Factors Affecting Early Bowel Complications (Univariate Analysis)

Factors	No	Early Complication Rate(%)	P-value
Age			
<60	11/37	29.7	
60	19/29	65.5	0.001
Stage			
Ib1, IIa (small)	6/21	28.6	
Ib2, IIa (large) IIb, IVa	24/45	53.3	0.05
Hypertension			
yes	3/ 8	37.5	
no	27/58	46.6	ns
Diabetes			
yes	2/ 5	40.0	
no	28/61	45.9	ns
Pelvic Inflammatory ds			
yes	1/ 3	33.3	
no	29/63	46.0	ns
Previous surgery			
yes	6/ 8	75.0	
no	24/58	41.4	0.001

Table 5. Risk Factors Affecting Early Bowel Complications (Multivariate Analysis)

Factors	Relative Risk	P-value
Age		
60 vs <60	1.87	0.03
Stage		
advanced vs early	1.62	ns
Hypertension		
yes vs no	0.91	ns
Diabetes		
yes vs no	0.81	ns
Pelvic Inflammatory ds		
yes vs no	0.61	ns
Previous surgery		
yes vs no	2.02	0.01

crypt abscesses composed almost entirely of eosinophils. Clinically most of early symptoms is expressed as a diarrhea, the cause of which is usually explained by various factors including failure of water and salt reabsorption in the colon, altered bile reabsorption by the injured ileum, and alterations in the intestinal bacterial flora.[6, 8]

But until now, few studies have been undertaken clinically to survey early bowel complications in cervical cancer patients. Crook et al reported acute radiation enteritis, characterized by abdominal cramping and diarrhea, occurred in 75% of patients and usually began in the second or third week of therapy[9] and Kim et al mentioned 46% of patients complained of mild or moderate degree of early bowel complication during treatment.[10] Bourne et al showed 11.3% (157) incidence of early serious radiation complications (grade 3, 4) in the 1390 patients followed at the Queensland Radium Institute. In four instances these resulted in death of the patients (a mortality rate of 0.3%).[11] In our study, 46% of patients experienced early bowel complications, most of which were grade 1 or 2 diarrhea and there was no mortality case.

The risk factors related to the development of early complications have rarely been analyzed, either. Jampolis et al showed that the severity of the early complications was proportional to the irradiated volume and recommended minimizing the volume of bowel irradiated to reduce bowel injury.[12, 13] In Bourne's study which dealt with only serious early complications, patients having "non-standard" radium insertions had a significantly higher early complication rate, compared with those patients having "standard" insertions (13.9% vs 9.0%, $P<0.01$) and the advanced stage was a significant risk factor, too. However, no association with the incidence of early complications was demonstrated for the following factors : patient age, history of previous abdomino- pelvic surgery, degree of tumor differentiation, the shape of central lead shielding or average rectal dose.[11] In our study, the incidence of early complications significantly correlated with an old age and a history of previous abdomino-pelvic surgery($P<0.05$) and the severity of early complications has a tendency to correlate with same factors. So to speak, early bowel complications were associated with conditions (i.e. old age, previous surgery) restricting the normal movement of intestine in and out of the usual treatment portals or compromising the blood supply of the bowel in some way. We can also guess role of external radiation dose from the fact that all of the grade 3, 4 complications occurred after 50.4 Gy external radiation dose. In contrast to the study of Bourne, we were unable to analyze all other item recorded for each patient. viz, parametrial boost, shape of central lead shielding, external dose, A point dose, geometry of ICR, rectal dose (Gy, TDF, BED) and so forth because in our study, most of complications were mild grade 1 or 2 complications which developed during external radiotherapy and severe complications occurred in only 5 patients.

The another controversial issue of the early complication is

what relationship exists between the early and late bowel complications. It is well known the incidence and severity of late complications tend to increase as the early radiation reaction becomes more severe. [14] But it is also appreciated that the absence of an early reaction does not ensure that a late complication will not occur. In the Bourne's study, the overall incidence of late complications was 3.6% (28/784). There was an 8.2% (7/85) incidence of late complications in those patients who had experienced early complications, compared with 3.0% (21/699) incidence of late complications in patients without early complications. This resulted in a relative risk of 2.7 (8.2%/3.0%) of developing a late complication, given survival after an early one ($P<0.05$). [11] Kline et al also reported a relationship between early radiation reactions and subsequent complications involving the gastrointestinal tract in the study of 410 patients. [15] On the contrary, recent radiobiologic evidence suggests that the   /   ratio for late responding tissues is relatively smaller than for early responding tissues and target cells of early and late complications may be separate entities. [16] Ha et al reported that the frequency of late complication was not related with early symptoms [17] and Rubin suggested that acute reaction is not predictive of chronic bowel damage. [18] Now it is generally accepted that acute reaction during therapy bears no relation to late effects such as stricture and ulceration.

Of our five patients with severe complications, treatment was interrupted in three patients and overall treatment time is prolonged about 2 weeks. All three patients experienced pelvic recurrences within post-irradiation 10 months. Despite advanced stage, there was a possibility that protracted overall treatment time had a dismal effect on treatment outcome. Mendenhall et al reported a trend toward decreased pelvic control with increasing treatment time beyond 60 days for tumors 6 cm or large. [19] Keane et al confirmed this in a multivariate analysis of 853 patients with cervical cancer. Treatment time was a predictive factor of pelvic control ($P=0.0001$), with evidence for accelerated tumor repopulation occurring about 37 days. The slope of isodose line was 0.17 Gy per day, indicating the daily dose increment required for prolongation of treatment beyond 37 days. The loss of local control per day of treatment prolongation was 1.2% for all stages combined. [20] Thus any unplanned interruptions or delays due to early complications during treatment should be avoided.

Innovative techniques using three-dimensional conformal treatment planning and symptomatic therapy is helpful in reducing subjective distress, maintaining performance status during the acute reaction period and finishing scheduled treatment on time. A low residue and low fat diet combined with an antiperistaltic drug such as loperamide or cholestyramine or kaolin, is often sufficient to relieve diarrhea. Sucralfate (aluminium hydroxide complex of sulfated sucrose), previously used in the treatment of gastric ulcer, was tested in a placebo-controlled randomized study on 70 patients undergoing irradiation for prostate or bladder cancer. [21] It was found that the patients in the sucralfate group displayed significantly less problems with frequency of defecation, mucus, and blood in the stools compared with the placebo group. There was also a lower intake of loperamide and the weight decrease was less pronounced in the sucralfate group. The earlier proposed mechanisms of action (eg, protection of denuded mucosa, cytoprotective properties, binding bile acids) seem adequate to explain the effects of sucralfate. A recent study showed that a suspension or supernatant of intestinal cells injected in the intestinal lumen of mice after whole body irradiation was found to increase the number of microcolonies. This suggests that a humoral factor available in the intestine may stimulate accelerated repopulation of intestinal mucosa and can be used to prevent early bowel complication. [22]

In conclusion, 46% of patients experienced early bowel complications, most of which were grade 1 or 2 and relieved spontaneously or by medication. The patients with an old age or a previous surgery have a high probability of early complications and they may be less compliant with planned radiotherapy. So more careful precaution is necessary for these patients.

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IB1   IIA   41.4Gy   30Gy   A   50.4Gy

24Gy   .   EORTC/RTOG morbidity criteria

90   .

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_____ :   66   30 (46%)   25 (38%)   grade 1, 2

4 (6%)   grade 3, 1 (2%)   grade 4   .   3

10   41%   .

3   2   3

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_____ : 46%   ,

(compliance)

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