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Efficacy of Chemoradiotherapy on Pain Relief in Patients with Intrapelvic Recurrence of Rectal Cancer

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Purpose: To assess the efficacy of chemoradiotherapy on pain relief in patients with intrapelvic recurrence of rectal cancer.

Methods: The records of 30 patients treated with radiotherapy with or without chemotherapy for intrapelvic recurrence of rectal cancer between September 1993 and February 1999 were retrospectively reviewed. There were 17 patients in the chemoradiotherapy (CRT) group and 13 patients in the radiotherapy alone (RTA) group. Simultaneous extrapelvic distant metastases were found in 11 patients in the CRT group and in seven patients in the RTA group. Radiotherapy was administered with a median total dose of 50 Gy in both groups. In the CRT group, 15 patients received 5-fluorouracil by continuous infusion and two patients received irinotecan in a biweekly infusion schedule during the course of radiotherapy. The response rate and duration of pain relief were evaluated and were compared between the two groups.

Results: The response rate of pain relief in the CRT and RTA was 100 and 77%, respectively. The median duration of pain relief in the CRT and RTA groups was 7.8 and 4.0 months, respectively and there was a significant difference between the two groups ($P = 0.019$). The median survival time from the start of radiotherapy was 15.1 and 9.3 months in the CRT and RTA groups, respectively, and there was a significant difference between the two groups ($P = 0.046$).

Conclusions: The results suggest that chemoradiotherapy for intrapelvic recurrence of rectal cancer for the purpose of pain relief appears to be more effective than radiotherapy alone.

Key words: rectal cancer – local recurrence – radiotherapy – chemoradiotherapy – pain relief

INTRODUCTION

Local recurrence rates after surgery alone in patients with rectal cancer have been reported to be 5–40% (1–4). In an attempt to improve local control and survival, pre- or postoperative chemoradiotherapy has been administered (5–7). Although only surgery has a curative potential for local recurrence, resection is often not feasible and a second locoregional recurrence after resection of a recurrent tumor was observed in >50% of cases (8). Radiotherapy for inoperable locally recurrent rectal cancer was reported to be effective for symptom control such as pain and bleeding (9,10). However, the median duration of symptom control after radiotherapy for local recurrence is short, ranging from 3 to 6 months (11,12) and it is not satisfactory for the patients. Objective tumor regression after radiotherapy is rarely achieved and the median survival time has been reported to be 12–18 months and <5% of patients have survived 5 years (13). While most patients usually develop and die of distant metastasis, it is important to control symptoms such as pain with respect to quality of life. In addition, the usefulness of chemoradiotherapy for local recurrence has been reported, but it is controversial with regard to symptom control and survival (9,14–18). In the present study, we assessed the efficacy of chemoradiotherapy on pain relief in patients with intrapelvic recurrence of rectal cancer.

PATIENTS AND METHODS

PATIENTS

The records of 30 consecutive patients treated with external-beam radiotherapy with or without chemotherapy for intrapelvic recurrence of rectal cancer for the purpose of pain control at the National Cancer Center Hospital East between September 1993 and February 1999 were retrospectively reviewed. There were 17 patients in the chemoradiotherapy (CRT) group

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and 13 patients in the radiotherapy alone (RTA) group. RTA was indicated for patients who were treated before 1998 or already had disease progression after treatment with systemic infusion of 5-fluorouracil (5-FU) and irinotecan (CPT-11). In the CRT group, three patients had been treated with chemotherapy consisting of intravenous infusion of 5-FU or CPT-11 before initiating radiotherapy. No patients in either group had previously been treated with radiotherapy to the pelvis.

Treatment

Radiation Therapy

Radiation therapy was performed with 2–4 individually shaped portals, 2 Gy per fraction, five fractions per week, using 10–21 MV X-rays. Treatment planning was performed using a CT simulator in all patients. Both gross tumor volume (GTV) and clinical target volume (CTV) were defined as recurrent intrapelvic tumors on CT images. Planning target volume (PTV) was defined as CTV + 10 mm in the lateral direction and cranio-caudal direction. Elective nodal irradiation was not performed. The total dose actually administered ranged from 22 to 51 Gy with a median dose of 50 Gy in the CRT group and from 12 to 60 Gy with a median dose of 50 Gy in the RTA group.

Chemotherapy

In the CRT group, 5-FU was administered concurrently during the course of radiation therapy as a continuous infusion throughout the week. The doses of 5-FU were determined by the patients' body surface areas; 2500 mg/week in 13 patients, 2000 mg/week in one patient and 3500 mg/week in one patient. The remaining two patients who had shown disease progression after the treatment with 5-FU received irinotecan (CPT-11) during the course of radiation therapy at a dose of 150 mg/m^2 in a 90 min infusion schedule repeated every 2 weeks.

Chemotherapy started from the first day of radiation therapy in six patients and in the other 11 patients chemotherapy started about 1 week before or after the start of radiation therapy.

Assessment of Clinical Outcome

Pain Relief

The effects on pain relief were compared before and immediately after completing the radiation therapy. Pain relief response was classified as follows: 'complete response' ('CR'), when pain disappeared without the use of an analgesic; 'partial response' ('PR'), when pain decreased or the daily dosage of the analgesic decreased; 'no change' ('NC'), when pain was unchanged and the dosage of the analgesic did not change; and 'progressive disease' ('PD'), when pain increased or the dosage of the analgesic increased, by taking the best point since the treatment started. The terms 'CR', 'PR', 'NC' and 'PD' were used as pain relief responses to distinguish them from those for the tumor response (CR, PR, SD and PD).

Duration of Pain Relief

The term duration of pain relief was defined as the interval between the initial date of radiation therapy and the date of the first documentation of increased pain or increased dosage of the analgesic after the best response of pain relief.

Intrapelvic Tumor Response

The response of the intrapelvic recurrent tumor was evaluated by measuring the tumor size by CT or MRI at 1–3 months after the completion of radiation therapy. Three of 30 patients could not be evaluated because there were no CT and MRI examinations after radiation therapy. We used the World Health Organization response criteria for measurable diseases without confirmation of a 4-week duration. Briefly, complete response (CR) was defined as the complete disappearance of all recurrent tumors, partial response (PR) as ≥50% reduction by the product of the longest cross-diameters on an image, stable disease (SD) as <25% reduction or increase and progressive disease (PD) as ≥25% increase. The status of distant metastases was not considered in this evaluation.

Toxicity

The toxicities were scored according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC Version 2.0). If the toxicity occurring >90 days after radiation therapy was considered to be due to radiation therapy, the toxicity was scored according to the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) late radiation morbidity scoring scheme.

Statistical Analysis

Survival and duration of pain relief were calculated by the Kaplan–Meier method. Survival was measured from the start of radiation therapy to the date of death from any causes. Duration of pain relief was measured from the start of radiation therapy to the date of the first documentation of increased pain or increased dosage of the analgesic after the best response of pain relief or death from any cause. The log rank test was used to assess the differences between the two groups. P values <0.05 were considered significant. All statistical analyses were performed using the StatView software package (Version 5.0; Abacus Concepts, Berkeley, CA).

RESULTS

The patient and treatment characteristics are summarized in Table 1. There were six patients in the CRT group and five patients in the RTA group who had direct invasion of the recurrent tumor to the sacrum. All patients had local pain at the start of radiation therapy. There were 10 patients in the CRT group and eight patients in the RTA group who received morphine for

Table 1. Patient and treatment characteristics

	CRT	RTA
No. of patients	17	13
Gender		
Male	11	10
Female	6	3
Age (years)	37–73	32–80
Median	61	56
Performance status		
1	13	13
2	4	0
Histology		
Adenocarcinoma	16	13
Mucinous carcinoma	1	0
Extrapelvic distant metastasis		
(+)	11	7
(–)	6	6
Size of recurrent tumor (cm)	3.0–14.0	3.0–9.0
Median	5.9	6.0
Previous chemotherapy		
(+)	3	4
(–)	14	9
Interval: initial surgery to recurrence (months)	1–153	4–60
Median	13	23
Interval: recurrence to radiotherapy (months)	1–16	1–22
Median	2	5
Total dose (Gy)	22–51	12–60
Median	50	50
Overall treatment time (days)	15–47	13–50
Median	37	39

CRT, chemoradiotherapy; RTA, radiotherapy alone.

pain control before the treatment; the median daily dose of morphine was 30 mg p.o. in both groups. The median follow-up period for patients was 9.3 months (range: 1.1–36.1 months). Twenty-eight of 30 patients completed the planned radiotherapy. The remaining two patients did not complete the radiotherapy: one patient in the CRT group discontinued the treatment at a dose of 22 Gy because of skin ulcers due to the progression of a recurrent tumor after he had achieved pain relief and another in the RTA group stopped at a dose of 12 Gy because of bowel obstruction. Of the 17 patients in the CRT group, 14 patients continued to receive chemotherapy until disease progression after the completion of radiation therapy. The median duration of chemotherapy after completion of radiation therapy was 4 months (range: 1.0–12.0 months). The other three patients discontinued receiving chemotherapy after the completion of radiation therapy, two owing to disease progression and one by refusal.

Table 2. Comparison of pain relief between CRT and RTA groups

Pain relief	CRT		RTA	
	No.	%	No.	%
'Complete response'	4	24	0	–
'Partial response'	13	76	10	77
'No change'	0	–	2	15
'Progressive disease'	0	–	0	–
Not evaluable	0	–	1	8

CRT, chemoradiotherapy; RTA, radiotherapy alone. The terms 'Complete response', 'Partial response', 'No change' and 'Progressive disease' were used for pain relief response to distinguish them from the tumor response.

Pain Relief

After the radiation therapy there were four 'CR' patients and 13 'PR' patients and the response rate of pain relief was 100% (17/17) in the CRT group. There were no 'CR' patients, 10 'PR' patients, two 'NC' patients and one non-evaluable (NE) patient and the response rate of pain relief was 77% (10/13) in the RTA group. The reason for the NE status was that the patient had grade 2 ileus at a dose of 12 Gy and was admitted to another hospital. There were no 'PD' patients during radiation therapy in either group (Table 2).

Duration of Pain Relief

Fig. 1 shows the duration of pain relief of the CRT and RTA groups. The median duration of pain relief in the CRT and RTA groups was 7.8 and 4.0 months, respectively. There was a significant difference in duration of pain relief between the two groups ($P = 0.019$). Regarding chemotherapy before initiating radiation therapy, the median duration of pain relief in the previous chemotherapy group and no previous chemotherapy group was 9.7 and 7.2 months, respectively. There was no difference in duration of pain relief between the two groups ($P = 0.92$).

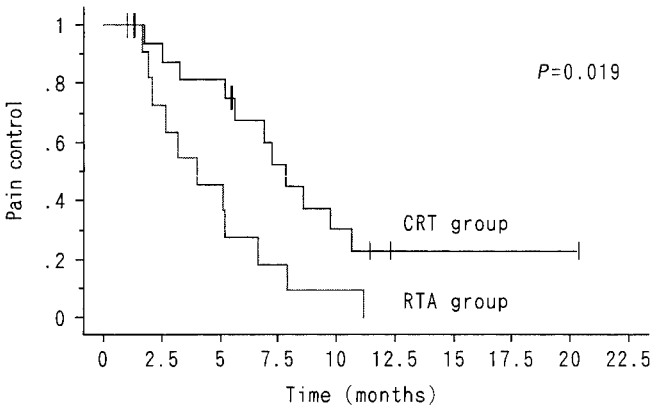

Figure 1. Duration of pain relief curves from the start of radiation therapy by treatment modality. CRT, chemoradiotherapy; RTA, radiotherapy alone. $P = 0.019$.

Table 3. Comparison of tumor response rate between CRT and RTA groups

Response	CRT		RTA	
	No.	%	No.	%
Complete response	0	–	0	–
Partial response	5	31	0	–
No change	11	69	11	100
Progressive disease	0	–	0	–

CRT, chemoradiotherapy; RTA, radiotherapy alone.

Intrapelvic Tumor Response

The response of the intrapelvic recurrent tumor of the two groups is shown in Table 3. Of the 27 evaluable patients, there were five PR patients and 11 SD patients with a response rate of 31% (5/16) in the CRT group, and there were 11 SD patients with a response rate of 0% (0/11) in the RTA group. No patients achieved CR in either group. Regarding the recurrent tumor size, there was no difference between the recurrent tumor size and tumor response ($P = 0.69$).

Summary of Toxicity

Toxicities greater than grade 2 are listed in Table 4. In the CRT group, grade 3 leukopenia and diarrhea occurred in one patient each during the course of radiation therapy and one patient developed a vesicovaginal fistula 11 months after completion of radiation therapy. In the RTA group, one patient developed a skin fistula 18 months after completion of radiation therapy and grade 3 hematuria occurred in one patient on the second day after the start of radiation therapy, which required transarterial embolization. Grade 4 ileus occurred in two patients in the CRT group at 4 and 7 months after completion of radiation therapy and in two patients in the RTA group at 2 and 11 months after completion of radiation therapy. Grade 4 ureteral obstruction occurred in one patient in the CRT group at 18 months after completion of radiation therapy and in three patients in the RTA group at 1, 3 and 4 months after completion of radiation therapy. These grade 3 fistula and grade 4 complications were considered to be due to disease progression, so we scored these toxicities occurring >90 days after radiation therapy according to NCI-CTC. No serious treatment-related toxicity was observed in either group. Also, there was no correlation between the field size and the toxicities greater than grade 2 ($P = 0.53$).

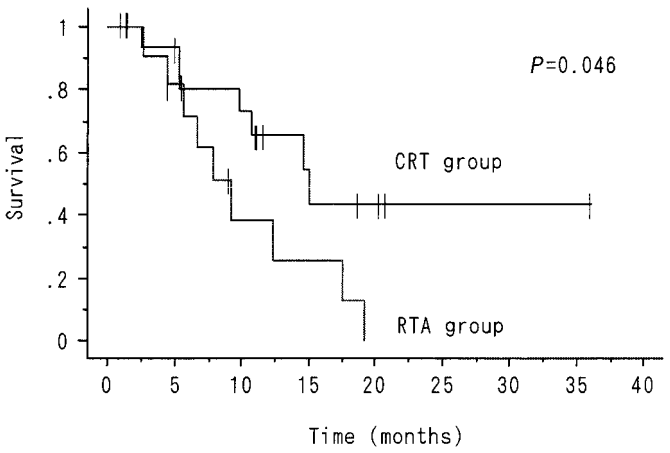

Figure 2. Overall survival curves from the start of radiation therapy by treatment modality. CRT, chemoradiotherapy; RTA, radiotherapy alone. $P = 0.046$.

Table 4. Summary of toxicity (grade ≥3 according to NCI-CTC)

Toxicity	CRT		RTA	
	No.	%	No.	%
Grade 3				
Leukopenia	1	6	0	–
Diarrhea	1	6	0	–
Fistula	1	6	1	8
Hematuria	0	–	1	8
Grade 4				
Ileus	2	12	2	15
Ureteral obstruction	1	6	3	23

CRT, chemoradiotherapy; RTA, radiotherapy alone.

Survival

Fig. 2 shows the overall survival of the two groups. Median survival times were 15.1 and 9.3 months in the CRT and RTA groups, respectively, with a significant difference between the two groups ($P = 0.046$). Regarding the recurrent tumor size, which is an important prognostic parameter, there was no difference between the recurrent tumor size and survival ($P = 0.18$).

DISCUSSION

We investigated the efficacy of chemoradiotherapy for intrapelvic recurrence of rectal cancer for the purpose of pain relief and showed that the median duration of pain relief in the CRT group was 7.8 months. This appeared to be a longer duration of pain relief compared with previous studies using treatment with radiation therapy alone that reported median durations of pain relief of 3–6 months (11,12). The reason for the prolongation of the duration of pain relief may be the enhanced radiosensitivity with chemotherapy and continuation of chemotherapy after radiation therapy. An early randomized study by Moertel et al. reported that the addition of 5-FU showed significantly longer survival rates than radiation therapy alone for locally unresectable colon and rectal cancer (15). Although several other randomized studies reported no benefit of the addition of chemotherapy in overall survival and symptom control and showed that there was an increase in

toxicity on the addition of chemotherapy (16–18), a low-dose continuous intravenous infusion of 5-FU was previously shown to be effective and had a low incidence of severe toxicity for colorectal cancer (19). In the present study there was no severe treatment-related toxicity with the combination of radiation therapy and continuous intravenous infusion of 5-FU and this might lead to favorable results.

Concerning radiation therapy, the dose–response relationship for symptom relief is controversial (9,10,12,20). Several studies reported that there was a dose–response relationship with radiation therapy in the management of recurrent rectal cancer (9,12). However, Wong et al. performed a systematic study and reported that there was no significant difference between patients receiving a dose of ≥45–50 Gy and patients receiving <45–50 Gy for pain relief (10). In the current study, the median total dose was 50 Gy in both groups and there were no severe treatment-related toxicities. It is suggested that a total dose of 50 Gy is feasible as a palliative treatment in terms of efficacy and toxicity even when combined with chemotherapy. Since 77% of the patients (23/30) received a total dose of 50 Gy and there were only three patients who received a dose of >50 Gy in this study, we did not analyze the dose–response relationship. Since this study was a retrospective comparison, there might be substantial biases caused by the differences in patients' backgrounds. In the CRT group, there were four patients with performance status (PS) 2 (24%), whereas no patients with PS 2 were included in the RTA group. Simultaneous extrapelvic metastases such as liver, lung and bone were more frequently seen in the CRT than in the RTA group: 11 patients (64%) in the CRT group and seven patients (54%) in the RTA group. The median interval from initial surgery to recurrence was 13 months in the CRT group and 23 months in the RTA group: Wong et al. reported in the systematic review that the shorter interval from initial surgery to recurrence was correlated with poor overall survival in the univariate analysis (10). There were no differences in the size of median recurrent tumor, radiation treatment regimens and median dosage of an analgesic between the two groups. Hence in this study there were more unfavorable patients in the CRT group than in the RTA group. Considering these biases and the treatment outcomes of both groups, CRT appears to be more effective than RTA in terms of pain relief and duration of pain relief. In addition, there was a significant difference in overall survival after the start of radiation therapy between the CRT and RTA groups (15.1 vs 9.3 months) in this study. Since 82% of the patients (14/17) in the CRT group continued to receive chemotherapy until disease progression after the completion of radiation therapy, the reason for this significant difference in overall survival may be due to systemic chemotherapy.

There was a tendency favoring the CRT group in tumor regression compared with the RTA group in the present study. However, there were no CR patients and the response rate was only 31% even in the CRT group, which was not a satisfactory result. To prolong the duration of pain relief, increasing the response rate may be beneficial and it is necessary to investigate the more effective chemotherapy regimens when combined with radiotherapy. It may be possible to increase the response rate by using combinations of 5-FU/CPT/leucovorin, which was recently reported to be effective for colorectal cancer (21) and new anti-cancer drugs such as oxaliplatin, S-1 and capecitabine, which were reported to be effective for gastrointestinal cancer (22–24). These regimens in combination with radiation therapy may be worth further investigation. For administering the radiation dose more intensively, intraoperative radiotherapy (IORT) and advanced external beam radiation techniques such as 3D conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy (IMRT) and proton beam therapy, which can reduce the dose to normal tissues such as the small intestine but increase the dose to recurrent tumors, may be useful. Suzuki et al. reported that the addition of IORT to external radiation therapy and maximal surgical resections was useful for locally recurrent rectal cancer without extrapelvic distant metastases (25). In this study there were eighteen patients (60%) who had extrapelvic distant metastases and the other patients were not recommended surgery owing to locally advanced recurrent tumor. Invasive procedures such as surgery and IORT may not be needed for palliative intent such as our cases. Further investigations of advanced external beam radiation techniques such as 3D-CRT and IMRT are needed to increase efficacy for pain relief with less toxicity.

In conclusion, we showed the efficacy of chemoradiotherapy for intrapelvic recurrence of rectal cancer for the purpose of pain relief.

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