EJSO (2004) **30**, 750–758

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EJSO
the Journal of Cancer Surgery

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Preoperative radio/chemo-radiotherapy in combination with intraoperative radiotherapy for T3-4Nx rectal cancer

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Accepted for publication 26 April 2004

Available online 5 June 2004

KEYWORDS
Rectal cancer; Chemo-radiotherapy; Intraoperative electronbeam radiotherapy; Sphincter preservation

Summary *Aims*. To analyse the results of a single institution experience of combined preoperative radio/chemo-radiotherapy and intraoperative electron-radiation therapy (IORT) for locally advanced rectal cancer and to compare the results with surgery alone retrospectively.

Methods. The study cohort comprised 99 patients with clinical T3-4NxM0 adenocarcinoma of the rectum who had received preoperative radio/chemo-radiotherapy, radical surgery, and IORT [Group I]. Until 1998, 67 patients were treated with radiation only [Group Ia], and after 1999, 32 patients were concurrently given tegafur and uracil (UFT) [Group Ib]. 68 patients with clinical T3-4NxM0 rectal cancer were treated with surgery alone [Group II].

Results. The median follow-up was 67 months in Group I and 83 months in Group II. Local recurrence rate was 2% in Group I, which was significantly lower than 16% in Group II ($p = 0.002$). Both disease-free survival and overall survival in Group I were significantly better than those in Group II ($p = 0.04$, $p = 0.02$, respectively). Sphincter preservation was possible in 78% in Group Ib, which was significantly more than 42% in Group Ia ($p = 0.002$).

Conclusions. The combined preoperative radio/chemo-radiotherapy and IORT for clinical T3-4Nx rectal cancer significantly reduces local recurrence and improves prognosis. Combination of preoperative radiotherapy and oral UFT improves the feasibility of sphincter-preservation.

Introduction

Local recurrence after surgery of rectal cancer is still a major problem. McCall et al. reviewed 10,465 cases in 51 papers from 1982 through 1992, and reported local recurrence rates ranging from 16% in Dukes B to 29% in Dukes C rectal cancer.[1] After the introduction of total mesorectal excision (TME), local recurrence rate was reported to be reduced to 5–19%,[2–4] however, Boley et al. reported it to be higher in Stage III disease (23%).[5] Recently, local recurrence rates have been reported to exceed 20%

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doi:10.1016/j.ejso.2004.04.012

in cases where the circumferential resection margin (CRM) was 1 mm or less in the resected specimen, suggesting that even with TME, the extent of resection is not sufficient in some cases.[6-8] Obtaining sufficient distance between tumour and CRM is often difficult and depends on the site and size of the tumours.

Preoperative or post-operative radiotherapy decreased local recurrence rate significantly. However, the effect on overall survival was marginal.[9] Combined modality adjuvant treatment with radiation therapy and 5-fluorouracil (5-FU)-based chemotherapy is more effective than either radiation therapy or chemotherapy alone.[10,11]

Intraoperative radiotherapy (IORT) has been used to treat primary unresectable colorectal cancer, residual colorectal cancer after resection, and recurrent colorectal cancer.[12,13] Good local control has been achieved when IORT was administered in combination with preoperative radiotherapy in patients evaluated as having undergone 'complete resection' or having 'microscopic disease,' although the reports were not based on randomised clinical trials.[14-16] IORT has conventionally been used to irradiate the tumour bed or only areas where the tumour was adherent or fixed.[14] However, local recurrences occur even in patients with no penetration of the tumour through the rectal wall. The dose distribution of 6–9 MeV electron beam is homogeneous at tissues 1–2 cm beneath the surface of the irradiated site. We developed a new concept to create the IORT-induced tumour-free margin just beneath the dissected surface of the pelvis. Therefore, we delivered electron beam, as uniformly as possible, to the dissected surface just after the removal of the rectum.[17,18]

This paper compares retrospectively the outcome of patients who received preoperative radio/chemo-radiotherapy combined with intraoperative electron beam radiation therapy (Group I) to that of patients who had surgery alone (Group II).

Patients and methods

The combined radio/chemo-radiotherapy group (Group I)

One hundred and four patients who had been diagnosed preoperatively as T3 or T4 (cT3-4), Nx, and M0 (UICC 1997) adenocarcinoma of the middle third or lower third of the rectum were treated with preoperative radio/chemo-radiotherapy, radical surgery, and IORT between January 1991 and December 2001. Tumour localisation was determined according to the criteria of the Japanese Society for Cancer of the Colon and Rectum.[19] The upper rectum is defined as the area between the promontory and the inferior margin of the 2nd sacral vertebra on the lateral view of a double contrast barium enema examination. The remaining rectum is divided into the middle and lower third of the rectum by the peritoneal reflection. The level of the peritoneal reflection corresponds to the level of the middle Houston valve on double contrast barium enema images. The length between the anus and the promontory was reported to be 17 cm in average.[20,21] Therefore, the middle or lower third of the rectum may correspond to the rectum within 10 or 12 cm from the anal verge in sigmoidoscopy. The initial evaluation included digital examination of the rectum, chest X-ray, colonoscopy, double contrast barium enema, and computed tomography of the abdomen and pelvis. Endorectal ultrasound has also been used since 1994.

During the study period, all patients were informed that preoperative radio/chemo-radiotherapy combined with IORT was not proved to have an additive benefit compared to surgery alone, and they were allowed to choose the treatment. All patients gave informed consent to receiving preoperative radio/chemo-radiotherapy, radical surgery, and IORT. Of the 104 patients, five were excluded from the study analysis because distant metastases or peritoneal metastases were found prior to or during surgery. The remaining 99 patients were judged to be curative and were designated as Group I (Table 1). In Group I, 67 patients from 1991 through 1998 were treated with preoperative radiation only (20 Gy in 10 fractions) (Group Ia), and 32 patients since 1999 received concurrent oral administration of tegafur and uracil (UFT) (Group Ib) (Table 2). UFT is an oral fluoropyrimidine which combines uracil and tegafur in a fixed molar ratio of 4:1.[22,23] Tegafur is a prodrug of 5-FU. Plasma 5-FU levels in patients administered oral UFT is comparable with those in patients receiving continuous 5-FU infusion.[24] UFT is active in colorectal cancer, and the oral administration and the improved safety profile offer advantages over both conventional and infusional 5-FU regimens.[25]

The surgical group (Group II)

Sixty-eight patients with curatively resected adenocarcinoma of the middle third or lower third of the rectum with clinical T-categories of 3 or 4 (cT3-4), Nx, M0 were treated by surgery alone

Table 1 Patient tumour and treatment characteristics

	Group I ($n = 99$)	Group II ($n = 68$)	p-value
Gender			
Male	80	47	0.12
Female	19	21	
Age (years)			
Mean ± SD	60 ± 10	61 ± 13	0.31
Tumour site			
Middle third	40	32	0.49
Lower third	59	36	
Tumour size (cm)			
Mean ± SD	4.3 ± 1.5	4.5 ± 2.1	0.18
pT-category			
0–1	3[a]	0	0.50
2	26	16	
3	58	43	
4	12	9	
pN-category			
0	66	41	0.59
1	22	16	
2	11	11	
pTNM-stage			
I	24[a]	13	0.56
II	43	28	
III	32	27	
Type of resection			
LAR[b]	53	37	1.0
APR[c]/exenteration	46	31	
Adjuvant chemotherapy	52	30	0.36
No adjuvant chemotherapy	47	38	
Median follow-up (months)	67	83	<0.001
Range	12–144	16–146	

Values are number of patients.
[a] Including two cases with pathologic complete regression.
[b] Low anterior resection.
[c] Abdominoperineal resection.

during the same period, and these patients were designated as Group II.

Surgery and post-operative therapy

Radical surgery was performed approximately 2 weeks after completion of the radiation schedule in Group I. Four senior surgeons were involved in both Groups. Although surgical procedure included TME proposed by Heald et al.[26] and preservation of the pelvic autonomic nerves, there were no strict criteria for selecting the type of surgical procedure.

No patient received post-operative radiotherapy. As for adjuvant chemotherapy for stage II or III colorectal cancer, oral fluoropyrimidines are generally used in Japan because they are very convenient.[27,28] Oral fluoropyrimidine including UFT was given for three months or longer to 52 patients in Group I and 30 patients in Group II, with no significant difference between the two groups (Table 1).

Follow-up

Patients were evaluated every 3–4 months for the initial 2 years, every 4–6 months for the next 2 years, and every 6–12 months thereafter, including CEA, abdominal CT or ultrasonography and chest X-ray. Double contrast barium enema or colonoscopy was performed every 2 years.

Table 2 Patient tumour and treatment characteristics in Group I

	Group Ia ($n = 67$)	Group Ib ($n = 32$)	p-value
Gender			
Male	50	30	0.03
Female	17	2	
Tumour site			
Middle third	24	16	0.26
Lower third	43	16	
Distance of tumour from anal verge			
Mean ± SD (cm)	5.4 ± 2.8	6.3 ± 2.7	0.12
Tumour size (cm) mean ± SD			
Before radiation[a]	5.0 ± 1.4	5.2 ± 0.9	0.46
Before surgery[a]	3.9 ± 1.3	3.4 ± 0.8	0.02
Resected specimen[b]	4.4 ± 1.5	3.9 ± 1.4	0.12
% Of tumour shrinkage			
Mean ± SD	22 ± 11	35 ± 11	<0.001
Response rate (%)	26	62	0.002
pT-category			
0–1	0	3[c]	0.09
2	18	8	
3	41	17	
4	8	4	
pN-category			
0	44	22	0.4
1	17	5	
2	6	5	
pTNM-stage			
I	14	10[c]	0.51
II	31	12	
III	22	10	
Type of resection			
LAR[d]	28	25	0.002
APR[e]/exenteration	39	7	

Values are number of patients.
[a] Length on the lateral view.
[b] Maximum diameter.
[c] Including two cases with pathologic complete regression.
[d] Low anterior resection.
[e] Abdominoperineal resection.

Perioperative morbidity was defined as occurring within 30 days of surgery or longer if the cause was clearly surgically related. Infection was defined as the presence of purulent drainage. Local recurrence was considered as any soft tissue or nodal failure in the pelvis, perineum, or groin. All other metastases were considered as distant metastases.

Preoperative external beam radiation therapy (EBRT) and chemotherapy

Preoperative radiation was delivered with 18-MV X-rays by a linear accelerator (Clinac 2100C, Varian Medical Systems, Inc. Palo Alto, CA, USA) using a two-field technique (anterior–posterior and posterior–anterior fields) in Group I. A dose of 20 Gy was administered at 2.0 Gy/day for 5 days for two consecutive weeks. The superior border of the radiation field was the L5/S1 junction and the lateral borders were 1 cm lateral to the widest bony margin of the true pelvic side walls. The inferior border was at the level of the inferior edges of the obturator foramina or 3 cm below the site of the tumour. The field size ranged from 15×15 to 16×18 cm.

UFT was orally administered at 400 mg/m^2/day of tegafur in two divided doses for 5 days per week for 4 consecutive weeks until surgery.

Intraoperative electron-radiation therapy (IORT)

After resection of the rectum, electron beam was administered with a linear accelerator according to our method reported previously.[17,18] The radiation dose was 20 Gy in five cases, 25 Gy in 20 cases and 15 Gy in 74 cases, and treatment energy of 6 MeV or 9 MeV was used. The ureters within the radiation field were protected by wrapping them with a 2-mm-thick and 8-cm-long lead shield. In patients who received sphincter-preserving surgery, the rectal stump was protected by positioning a 5-cm or 6.5-cm in diameter shield block made of lead (1-cm-thick) and aluminum (2-cm-thick).

Tumour size, percentage of tumour shrinkage and response rate

Tumour size was measured on the resected specimen. Percentage of tumour shrinkage was calculated based on the size on the lateral view of the double contrast barium enema examination before and after preoperative radio/chemo-radiotherapy. The measured value of tumour size on double contrast barium enema images was revised by the width of the first sacral vertebrae. A shrinkage of 30% or more was defined as response to treatment.

Statistical analysis

For statistical comparisons of the patient characteristics between the two groups, the chi-square test of independence, Fisher's exact probability test or unpaired-*t* test was used. Survival and disease-free survival curves were obtained by the Kaplan–Meier method and compared using the log-rank test.

Results

Patient characteristics

There were no significant differences between Group I and Group II with respect to gender, age, tumour site, or tumour size measured in the surgical specimen (Table 1). The minimum follow-up period was 12 months. The median follow-up period was 67 months in Group I and 83 months in Group II. The median follow-up period in Group I was significantly shorter because the number of cases in which preoperative radio/chemo-radiotherapy is employed has increased recently.

Tumour response and pathologic stage

The preoperative diagnosis in Group I was cT3-4, but the resected specimen included two cases of complete regression, one case of pT1, and 26 cases of pT2. There were no significant differences in pT, pN, and pTNM stages between the two groups (Table 1). Subgroup analysis with or without chemotherapy between Group Ia and Ib showed no significant difference in pT, pN, and pTNM stages, and downstaging due to the addition of chemotherapy was not clear (Table 2). The tumour size of Group Ib just before surgery was significantly smaller than that of Group Ia ($p = 0.02$) although tumour sizes before treatment were similar. The percentages of tumour shrinkage resulting from preoperative treatment and response rates were significantly greater in Group Ib than those in Group Ia ($p < 0.001$, $p = 0.002$, respectively).

Sphincter preservation (SP)

Sphincter-saving surgical procedure was performed in 54% in both Groups I and II (Table 1). In Group I, SP could be performed in 78% of Group Ib, which was significantly greater when compared to 42% of Group Ia ($p = 0.002$) (Table 2). In the limited cases where the tumours were located within 6 cm from the anal verge, SP was possible in four out of 41 cases (10%) in Group Ia and in eight out of 15 cases (53%) in Group Ib, the percentage of the latter being significantly greater ($p < 0.001$).

Toxicity

In Group I, grade 3 or 4 toxicity (NCI-CTC) due to preoperative radiotherapy or chemo-radiotherapy was not observed. Although the incidences of grade 1 or 2 leucopenia and nausea were significantly higher in Group Ib as compared with those in Group Ia, there was no difference in liver function test (Table 3).

Mortality and morbidity

There was one death (1%) in Group I and two deaths (3%) in Group II. The causes of death were acute cardiac failure in Group I, and pneumonia in Group II. The incidence of complication was 34% in Group I and 29% in Group II, wound infection being most frequent in both groups (Table 4).

Recurrence

Local recurrence was observed in two patients (2%)

Table 3 Acute toxicities by National Cancer Institute common toxicity criteria

1 ≤ Grade ≤ 2	Group Ia ($n = 67$)	Group Ib ($n = 32$)	p value
Leucopenia	11	13	0.02
Anaemia	29	19	0.2
Thrombocytopenia	5	5	0.36
AST (SGOT)	10	4	1
Diarrhoea	9	9	0.14
Nausea	8	16	<0.0001
Vomiting	0	0	
Stomatitis	0	0	

Values are number of patients.

in Group I and 11 patients (16%) in Group II; the rate in Group I was significantly lower ($p = 0.002$) (Table 5). In Group I, rate of local recurrence was 0% in stage II and 6% in stage III patients, whereas it was 11% and 30%, respectively, in Group II. Distant metastases occurred in approximately 20% of the patients in both groups.

Disease-free survival

Disease-free survival rate in Group I was significantly better than that in Group II ($p = 0.04$) (Fig. 1). The three year disease-free survival rates were 79% in Group I and 59% in Group II, and five year disease-free survival rates, 71 and 54%, respectively. When compared stage by stage, no significant difference was observed between the two groups.

Survival

Survival rate in Group I was significantly better than that in Group II ($p = 0.02$) (Fig. 2). Three year survival rates were 89% in Group I and 79% in Group II, and five year survival rates, 79 and 58%, respectively. When compared stage by stage, no significant difference was observed between the two groups.

Discussion

Surgical margin

The shortest distance from the outermost part of the tumour to the lateral resection margin (i.e. CRM) has been reported to be a crucial predictive factor of local recurrence in rectal cancer. Adam et al. have reported that in 25% of cases where the surgeons had assessed the procedure as curative intraoperatively, these cases turned out to have a histologically positive margin.[29] Recent studies showed that 20–30% of the cases actually would be histologically margin positive even with TME.[6,8]

Benefits of IORT

Our target sites of IORT were the resected surface of the pelvic wall that had been continuous to the CRM of this resected specimen in vivo, and the tissues 1–2 cm beneath it. The absorbed dose of electron beams is maximal at 1–2 cm below the irradiated surface. Therefore, the electron beams irradiated as uniformly as possible the entire dissected surface of the pelvic cavity after resection of the rectal cancer. We used IORT for patients with curatively resected rectal cancer since 1985

Table 4 Incidence of complications by treatment groups

	Group I ($n = 99$)	Group II ($n = 68$)	p-value
Small-bowel obstruction (requiring lysis)	0	1	0.41
Anastomotic leakage (requiring temporary colostomy)	6	3	0.74
Wound infection	23	8	0.09
Bleeding	3	1	0.65
Pneumonia	1	4	0.16
Acute cardiac failure	1	0	1
Cerebral infarction	1	0	1
Neurogenic bladder dysfunction	2	3	0.4

Values are number of patients.

Table 5 Site of first recurrence

	No. of cases	Loco-regional	Lung	Liver	Peritoneum	Lymph-node	Bone	Brain	Retroperitoneum
Group I									
Stage I	24[a]	0	1	0	0	0	0	0	0
Stage II	43	0	2	3	1	0	0	0	0
Stage III	32	2	4	5	0	2	0	0	0
Total	99	2	7	8	1	2	0	0	0
Group II									
Stage I	13	0	3	0	0	0	0	0	0
Stage II	28	3	2	1	0	1	0	1	1
Stage III	27	8	4	2	0	1	1	0	0
Total	68	11	9	3	0	2	1	1	1

[a] Including two cases with pathological complete regression.

and reported that the rate of local recurrence reduced from 11 to 3%. [17,18]

Benefits of combined preoperative radio/chemo-radiotherapy

Since 1991, we have combined preoperative radiotherapy with IORT, and from 1999 we have further employed preoperative concurrent chemo-radiotherapy with an oral fluoropyrimidine UFT. In Western countries, conventional schedule of preoperative radiation is a total dose of 45–50.4 Gy at 1.8–2.0 Gy/fraction, and its effectiveness for preventing local recurrence is confirmed by meta-analysis.[9] We used a dose of 20 Gy in 10 fractions for preoperative radiation. The biological effectiveness of single-dose IORT is considered the equivalent of two or three times that quantity of fractionated EBRT.[30] Thus if 15 Gy of IORT is added to a preoperative dose of 20 Gy, this should equal at least 50 Gy. Calvo et al. have reported that delivering 12.5 Gy of IORT to the presacral space intraoperatively after preoperative chemo-radiotherapy at 45–50 Gy yielded local recurrence rate of 3%.[31] The present study suggested that our treatment doses are sufficient for decreasing local recurrence without increasing complications in cases with resectable T3-4 rectal cancer.

The local recurrence rate of the combined radiotherapy group was 2%, which was significantly lower compared with 16% of the surgery-alone group ($p = 0.002$). However, no difference was observed in the rate of distant metastasis between the two groups, both being approximately 20%. Both the disease-free survival and overall survival were significantly better in the combined radiotherapy group compared with the surgery-alone group. Therefore, the decrease in local recurrence rate due to preoperative radio/chemo-radiotherapy may have led to the significantly better disease-free survival and overall survival. When compared by pathological stage, however, there was no stage-by-stage difference in disease-free survival and overall survival between the two groups. This suggests the need for appropriate post-operative adjuvant chemotherapy to decrease distant metastasis and to obtain further favorable outcome.

Benefits of chemo-radiotherapy and sphincter preservation (SP)

There have been reports that the possible cases of

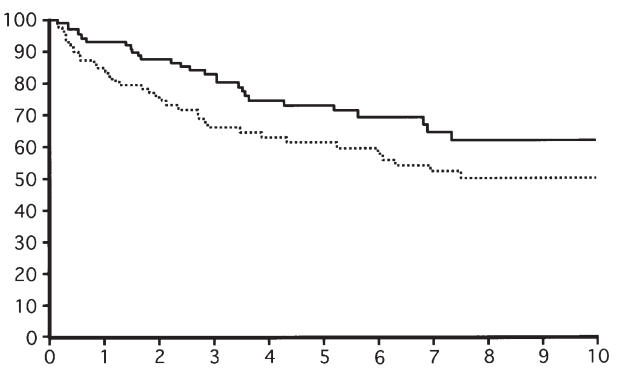

Figure 1 Disease-free survival in the Group I (—) and Group II (···) ($p = 0.04$).

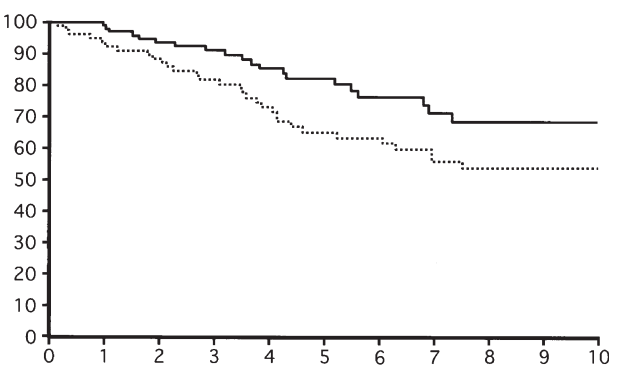

Figure 2 Overall survival in the Group I (—) and Group II (···) ($p = 0.02$).

SP due to preoperative adjuvant radiotherapy are likely to increase.[32,33] Furthermore, an oral fluoropyrimidine has been reported to be effective in preoperative chemo-radiotherapy.[34,35] UFT, an oral fluoropyrimidine, has been widely used in Japan, and its efficacy has been shown in a multicenter randomised trial.[27] We have demonstrated that administering UFT at 400 mg/m^2/day for 5 day a week with a rest period of 2 days serves as an adjuvant therapy for colorectal cancer that could be scheduled for 1 year administration with good compliance and safety profile,[30] as well as comparatively highly sustained 5-FU levels within the tumours, even during a rest period of 2 days.[36] Since 1999, we have administered UFT to 32 patients in combination with radiation, but no adverse reaction of grade 3 or 4 was observed. With our treatment schedule, toxicity due to preoperative radiation and chemoradiation was extremely mild, and there was no increase in mortality and morbidity compared to that of surgery alone. Subgroup analysis between the radiotherapy group (Group Ia) which received radiation only and the chemo-radiotherapy group (Group Ib) which received radiation and UFT shows that there were no differences in tumour size and the distance between the anal verge to the lower margin of tumour before preoperative radiation, whereas the percentage of tumour shrinkage was 35 $\pm$ 11% in the chemo-radiotherapy group, which was significantly greater when compared to 22 $\pm$ 11% in the radiotherapy group. The rate of implementing SP was 78% in the chemo-radiotherapy group, which was also significantly higher when compared to 42% in the radiotherapy group. Janjan et al. have reported that with preoperative concurrent chemo-radiotherapy of radiation at 45 Gy and 5-FU at 300 mg/m^2/day, SP was possible in 59% of all cases, and in 42% of the cases where the tumour was within 6 cm from the anal verge.[33] In the present series, similar results were obtained: SP was possible in 78% of all chemo-radiotherapy group and in 53% (10/19) of the cases where the tumour was within 6 cm from the anal verge.

Conclusions

Combination therapy that combines preoperative external beam radiation (20 Gy) and intraoperative radiation for cT3-4Nx rectal cancer shows significantly decrease in local recurrence rate and improves prognosis. Furthermore, chemo-radiotherapy that combines preoperative radiation and UFT is suggested to increase the feasibility of sphincter-preserving surgery without increasing severe adverse reactions.

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