

RAPID COMMUNICATION

Three-dimensional conformal radiotherapy combined with FOLFOX4 chemotherapy for unresectable recurrent rectal cancer

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Abstract

AIM: To investigate the effect of three-dimensional conformal radiotherapy (3-DCRT) in combination with FOLFOX4 chemotherapy for unresectable recurrent rectal cancer.

METHODS: Forty-eight patients with unresectable recurrent rectal cancer were randomized and treated by 3-DCRT or 3-DCRT combined with FOLFOX4 chemotherapy between September 2001 and October 2003. For the patients without prior radiation history, the initial radiation was given to the whole pelvis by traditional methods with tumor dose of 40 Gy, followed by 3-DCRT for the recurrent lesions to the median total cumulative tumor dose of 60 Gy (range 56-66 Gy); for the post-radiation recurrent patients, 3-DCRT was directly given for the recurrent lesions to the median tumor dose of 40 Gy (36-46 Gy). For patients in the study group, two cycles chemotherapy with FOLFOX4 regimen were given concurrently with radiotherapy, with the first cycle given simultaneously with the initiation of radiation and the second cycle given in the fifth week for patients receiving conventional pelvis radiation or given in the last week of 3-DCRT for patients receiving 3-DCRT directly. Another 2-4 cycles (average 3.6 cycles) sequential FOLFOX4 regimen chemotherapy were given to the patients in the study group, beginning at 2-3 wk after chemoradiation. The outcomes of symptoms relieve, tumor response, survival and toxicity were recorded and compared between the study group and the control group.

RESULTS: For the study group and the control group, the pain-alleviation rates were 95.2% and 91.3%

($P > 0.05$); the overall response rates were 56.5% and 40.0% ($P > 0.05$); the 1-year and 2-year survival rates were 86.9%, 50.2% and 80.0%, 23.9%, with median survival time of 25 mo and 16 mo ($P < 0.05$); the 2-year distant metastasis rates were 39.1% and 56.0% ($P = 0.054$), respectively. The side effects, except peripheral neuropathy which was relatively severer in the study group, were similar in the the two groups and well tolerated.

CONCLUSION: Three-dimensional conformal radiotherapy combined with FOLFOX4 chemotherapy for unresectable recurrent rectal cancer is a feasible and effective therapeutic approach, and can reduce distant metastasis rate and improve the survival rate.

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Key words: Rectal neoplasms; Radiotherapy; Chemotherapy

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INTRODUCTION

Despite all previous efforts at radical curative resection and multidisciplinary treatment, locally recurrent rectal cancer (LRRC) occurs in up to one third of patients^[1-3]. A curative treatment is possible only when local recurrences represent limited disease that may be amenable to surgical re-excision^[4,5]. Unfortunately, most patients with LRRC will be excluded from curative surgery on the basis of medical fitness, the presence of distant metastasis, locally unresectable disease or an unwilling to accept the considerable associated morbidity and mortality. In these patients, palliative intervention still may be required^[6].

Patients with unresectable LRRC are often treated with nonsurgical palliation, including radiation therapy, chemotherapy and chemoradiation. Radiation has been confirmed as an effective method to palliate the symptoms and dose-response relationship between radiation doses and subjective response of LRRC has been revealed by some studies^[7-10]. The strategy to elevate the radiation dose by adopting

new techniques, such as three-dimensional conformal radiotherapy (3-DCRT) or intensity-modified radiotherapy (IMRT), is needed to improve the local control of LRRC. It is also reasonable to combine chemotherapy into the multi-modality treatment for LRRC patients because systemic metastasis is a common problem. We designed herein a randomized, controlled study to compare the efficacy and the toxicities of exclusive 3-DCRT and 3-DCRT combined with FOLFOX4 chemotherapy for patients with unresectable LRRC.

MATERIALS AND METHODS

Patients and characteristics

Between September 2001 and October 2003, 48 patients with unresectable LRRC were randomized and treated by 3-DCRT at the Radiation Oncology Department, Sir Run Run Shaw Hospital. Twenty-five cases among them were treated by exclusive 3-DCRT and defined as the control group, while the other 23 cases received 3-DCRT combined with FOLFOX4 regimen and were defined as the study group. Table 1 shows the clinical data and pathologic characteristics with the initial operation. The diagnosis of local recurrence of rectal cancer mainly depended on imaging exam. Of 44 patients, presacral masses were detected by pelvis B-ultrasound, computerized tomography (CT) or magnetic resonance imaging, 10 cases were confirmed by biopsy pathological result. Thirty-five cases among them had solitary presacral mass, 9 cases (5 cases in the study group and 4 cases in the control group) had multiple masses or accompanied with adjacent lymph nodes metastases, but all the lesions can be dealt as a whole target. Of the other 4 cases, solitary masses in the pelvic sidewall were found by imaging exam. All the cases were consulted by radiologists and surgeons and evaluated as unresectable. Systemic examination was carried out to exclude distant metastasis. The median interval between local recurrence and initial operation was 15 (range 7-42) mo. Eighteen cases among the study group and 20 cases among the control group had received peri-operative radiotherapy with dose of 40-50 Gy. Twenty cases among the both groups had received 5-fluorouracil (5-Fu)-based peri-operative chemotherapy.

Treatment

For the patients without prior radiation history, the initial radiation was given to the whole pelvis by traditional methods with tumor dose of 40 Gy, followed by 3-DCRT for the recurrent lesions to the median total cumulative tumor dose of 60 Gy (range 56-66 Gy); for the post-radiation recurrent patients, 3-DCRT was directly given for the recurrent lesions to the median tumor dose of 40 Gy (36-46 Gy). The entire pelvis was irradiated with 10 MV photons using AP/PA portals or PA portal and two lateral wedged portals. The schedule was once daily, 5 times a week, using 200 cGy fractions, to a final dose of 40 Gy. Belly board was used to reduce the volume of small bowel irradiated. For 3-DCRT, all patients had a CT scan in the treatment position immobilized by thermoplastic molds for treatment planning purposes. Using the CT data set, the clinical target volume defined as the gross tumor volume with

Table 1 Clinical and pathologic characteristics of the patients

Variables	Control group (n = 25)	Study group (n = 23)
Age (yr): Median (range)	62 (36-70)	62 (40-72)
Sex		
Male	17	14
Female	8	9
Dukes' stage of initial lesion		
A	1	1
B	7	5
C	17	17
Tumor pathologic type		
Well and moderately differentiated adenocarcinoma	19	17
Mucinous adenocarcinoma	4	3
Signet ring cell carcinoma	2	3
Recurrent sites		
Presacral	23	21
Pelvic sidewall	2	2

No significant differences in clinical or pathologic variables between the two groups were observed.

5-mm margin was delineated and confirmed by radiologists, radiation oncologists and radiotherapy physicians. An additional 5-10 mm was added for planning target volume. Radiotherapy treatment planning was performed using Pinnacle3 3-D conformal radiation treatment planning system. Three to seven fields with individualized blocks derived from beam's-eye-view were used to implement the 3-DCRT. PTV was surrounded by 90% isodose curvature. Three-dimensional CRT was delivered with 10 MV photon and conventional fractionation: once daily, 5 times a week, 200 cGy per fraction. For patients in the study group, two cycles chemotherapy with FOLFOX4 regimen were given concurrently with radiotherapy, with the first cycle given simultaneously with the initiation of radiation and the second cycle given in the fifth week for patients receiving conventional pelvis radiation or given in the last week of 3-DCRT for patients receiving 3-DCRT directly. Another 2-4 (average 3.6) cycles sequential FOLFOX4 regimen chemotherapy were given to the patients in the study group beginning at 2-3 wk after chemoradiation. FOLFOX4 regimen comprised of intravenous injection of oxaliplatin at a dose of 85 mg/m² on d 1, intravenous injection of leucovorin at a dose of 300 mg/m² and intravenous injection of 5-Fu at a dose of 400 mg/m² and continuous intravenous injection of 5-Fu at a dose of 600 mg/m² on d 1 and d 2.

Evaluation of patients

Patients were observed at 3-mo intervals for 18 mo after the completion of therapy and every 6 mo for 3 years. All patients were followed up till December 2004, with follow-up duration of 6-39 (median 23) mo, except two who were lost to follow-up and presumed dead. Assessment of pain was scored from 0 (no pain) to 10 (as bad as you can imagine) by numeric rating scale. If the pain score decreased more than a half, good pain palliation was considered. Assessments of tumor dimensions by CT scan were performed before the start of treatment and repeated

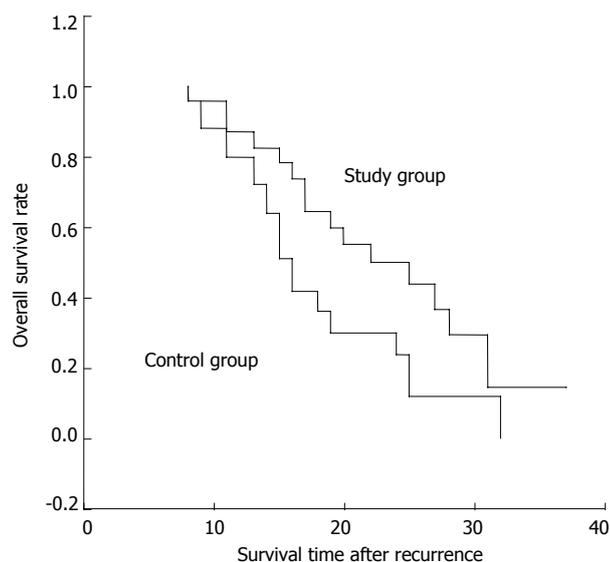


Figure 1 Overall survival curves of patients in the two groups. Five patients survived in the control group, and 8 patients survived in the study group.

1 mo after the end of 3-DCRT. Tumor objective responses were classified as complete response, partial response, stable disease and progression disease based on standard World Health Organization (WHO) criteria. The data of toxicity were ranked according to the WHO evaluation.

Statistical analysis

Survival estimates were calculated using Kaplan-Meier curves and a two-sided log-rank test was used to compare survival curves. χ^2 test was used to determine the difference of pain palliation rates, objective response rates and distant metastasis rate. P value < 0.05 was considered statistically significant.

RESULTS

Good pain palliation rate was 95.2% (20/21) in the study group and 91.3% (21/23) in the control group, with median palliation time of 13 d (range 6-58 d) and 15 d (range 8-65 d), respectively ($\chi^2 = 0.261$, $P = 0.609$).

The overall objective response rate in the study group was 56.5% (1 complete response, 12 partial responses), while that in the control group was 40.0% (0 complete response, 10 partial responses) ($\chi^2 = 1.283$, $P = 0.257$).

Figure 1 shows overall survival of the two groups. In the study group, 1-year and 2-year overall survival rates were 86.9% and 50.2%, while those of the control group were 80.0% and 23.9% with median survival time of 25 mo and 16 mo, respectively (Log-rank = 4.01, $P = 0.045$).

Interestingly, 2-year distant metastasis rates of the two groups were 39.1% and 56.0% with median distant metastatic time of 16 (range 7-26) mo and 10 (range 3-23) mo, respectively ($\chi^2 = 3.715$, $P = 0.054$).

Toxicities of patients were scored according to WHO scale. A detailed description of acute toxicities was given in Table 2. The main toxic reactions of the control group patients included diarrhea, rectal tenesmus, perianal area skin reaction and bone marrow suppression. The main toxicities of the study group patients were similar but

Table 2 WHO scale for acute toxicities

Toxicity	Grade	Control group	Study group	χ^2 value
Leukopenia	I	6	10	3.41
	II	2	8	
	III	0	3	
	IV	0	0	
GI tract	I	8	3	0.66
	II	5	10	
	III	5	6	
	IV	1	2	
Proctitis	I	10	9	0.01
	II	6	8	
	III	3	3	
	IV	0	0	
Skin	I	5	3	0.00
	II	8	9	
	III	12	11	
	IV	0	0	
Peripheral neuropathy	I	0	10	1.09
	II	0	4	
	III	0	1	
Bladder	I	12	11	0.27
	II	6	8	
	III	2	1	
	IV	0	0	

$P > 0.05$. P value was calculated by subgroups for toxicity grade ≥ 3 .

relatively severe peripheral neuropathy. No toxicity-related death was observed in both the groups. In the study group, radiotherapy of 3 patients was interrupted and delayed for 2-4 d due to severe diarrhea and rectal tenesmus, and the 2nd cycle chemotherapy of 1 patient was canceled due to severe bone marrow suppression. In the control group, radiotherapy of 2 patients was interrupted and delayed for 2 and 3 d, respectively, due to severe diarrhea and rectal tenesmus. No severe late toxicity was observed in both groups in the follow-up duration.

DISCUSSION

The optimal treatment for locoregionally recurrent rectal cancer after curative surgery has not yet been defined^[5,11,12]. Most of the recurrent rectal cancers are not resectable and require nonsurgical approaches. Multimodality treatment would probably offer the best result^[13]. In the past, patients with locally unresectable recurrent rectal cancer were assumed incurable and received mostly palliative therapy. Traditional radiotherapy and chemotherapy given with palliative goal have been confirmed good palliation result of symptoms, such as local pain and bleeding with unknown effect on survival. Noticeably, several series have found a dose-response relationship of radiotherapy for symptoms control^[9,14,15]. Some of them revealed the relationship also for local control and survival rate^[9]. Sanfilippo *et al*^[16] reported that despite aggressive multimodality therapy, a high rate of pelvic recurrence occurred in patients with clinically staged T₄ disease, and regional disease recurred almost exclusively in the radiation field. Under such circumstances, there is a significant need to adopt new techniques, such as intraoperative radiation therapy, brachytherapy and 3-DCRT, to safely deliver tumoricidal dose of radiation in an attempt to improve the local control^[17-20].

Moreover, 3-DCRT allows more accurate definition of target volume and anatomy of critical normal structures. This technique focuses radiation to specific sites of disease, thereby minimizing injury to normal tissues. Higher doses of irradiation can be delivered by this technique to produce better tumor control without increasing the probabilities of particular sequela. It is controversial that whether previously irradiated LRRC patients could receive reirradiation and whether the reirradiation is of any value. Several investigators reported that high doses of reirradiation could be delivered with acceptable risks without prohibitive long-term side effects in patients with LRRC and could result in surgical salvage and long-term survival in selected patients^[10,21,22]. This may be related to the location of local recurrence. A multicenter analysis of 123 patients with recurrent rectal cancer within the pelvis revealed that recurrent tumors were mainly situated in the posterior part of the bony pelvis and patients received abdominoperineal resection had a significantly more extension of recurrent tumors in the inferior parts of the pelvis comparing to those patients received low anterior resection^[23]. There are fewer organs at risk in the lower and posterior pelvis. The usual local recurrent location of rectal cancer and 3-DCRT technique make it feasible to deliver higher radiation dose comparing with conventional radiation or to reirradiate with high dose for patients suffered from LRRC. In this study, we treated all patients with 3-DCRT or 3-DCRT boost to relatively higher dose, resulting in good palliation of pain in 93.2% (41/44) patients, the objective response rate in 47.9% (23/48) patients, and well tolerated toxicities. Thus we can roughly draw a conclusion that 3-DCRT for LRRC patients is feasible and effective.

It is now generally accepted that exclusive radiotherapy plays a minor role in improvement in survival unlike its major role in palliation of symptoms and improvement of local control for rectal cancer. Combined modality treatment is the recommended standard adjuvant therapy for patients with locally advanced rectal cancer. Currently, most adjuvant therapy includes chemotherapy^[24]. Traditional chemotherapy or chemoradiation focuses on 5-Fu-based regimens, which have been confirmed to be effective. In our previous study, we have reported that preoperative radiotherapy combined with full course chemotherapy (LV + 5-Fu + 5'DfuR) is effective and safe^[25]. Because of the clinical appliances of oxaliplatin during the recent years, substantial progress has been made in chemotherapy of rectal cancer. Chemotherapy with oxaliplatin combined with 5-Fu, such as FOLFOX4 regimen, is more effective and has become the standard treatment for advanced stage colorectal cancer^[26]. In the United States, using similar chemotherapy regimens as adjuvant therapy has been approved. The advantages of oxaliplatin, such as its mild toxicities in gastrointestinal tract and bone marrow suppression, make it feasible to combine it with radiotherapy, especially when new radiation techniques, such as 3-DCRT, are applied. Local recurrence of rectal cancer is more common in the locally advanced patients, who have received 5-Fu-based chemotherapy in primary treatment, as exhibited in this study. For these patients, chemotherapy using more effective new drugs without cross-resistance is mandatory. In this study, we attempted to adopt 3-DCRT

combined with FOLFOX4 chemotherapy for unresectable LRRC. The tumor response rates were similar in the both groups, but the 1- and 2-year overall survival rates and median survival time of the study group were better than those of the control group. Further analysis of the data revealed that the distant metastatic rate and median distant metastatic time of the study group marginally surpassed those of the control group ($P=0.054$). We postulate that for LRRC patients receiving radiation and the combination of chemotherapy with FOLFOX4 regimen can reduce distant metastatic rate, delay the occurrence of distant metastasis and then influence the overall survival rate, even majority of the patients have received full course 5-Fu-based chemotherapy. In summary, 3-DCRT combined with FOLFOX4 chemotherapy appears to be a feasible and effective treatment for unresectable LRRC. Larger-scale studies are needed to evaluate the potency of this kind of therapeutic strategy.

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