• COLORECTAL CANCER •

Pre-operative radiochemotherapy of locally advanced rectal cancer

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Received: 2002-08-01   **Accepted:** 2002-11-19

Abstract

AIM: To evaluate results of pre-operative radiochemotherapy followed by surgery for 15 patients with locally advanced un-resectable rectal cancer.

METHODS: 15 patients with advanced non-resectable rectal cancer were treated with pre-operative irriadiation of 40-46 Gy plus concomitant chemotherapy (5-FU+LV and 5'-DFuR) (RCS group). For comparison, 27 similar patients, treated by preoperative radiotherapy (40-50 Gy) plus surgery were served as control (RS group).

RESULTS: No radiochemotherapy or radiotherapy was interrupted and then was delayed because of toxicities in both groups. The radical resectability rate was 73.3 % in the RCS group and 37.0 % (P=0.024) in RS group. Sphincter preservation rates were 26.6 % and 3.7 % respectively (P=0.028). Sphincter preservation rates of lower rectal cancer were 27.3 % and 0.0 % respectively (P=0.014). Response rates of RCS and RS groups were 46.7 % and 18.5 % (P=0.053). The tumor downstage rates were 8 (53.3 %) and 9 (33.3 %) in these groups (P=0.206). The 3-year overall survival rates were 66.7 % and 55.6 % (P=0.485), and the disease free survival rates were 40.1 % and 33.2 % (P=0.663). The 3-year local recurrent rates were 26.7 % and 48.1 % (P=0.174). No obvious late effects were found in either groups.

CONCLUSION: High resectability is possible following pre-operative radiochemotherapy and can have more sphincters preserved. It is important to improve the quality of the patients' life even without increasing the survival or local control rates. Preoperative radiotherapy with concomitant full course chemotherapy (5-Fu+LV and 5'-DFuR) is effective and safe.

Sun XN, Yang QC, Hu JB. Pre-operative radiochemotherapy of locally advanced rectal cancer. *World J Gastroenterol* 2003; 9 (4): 717-720

http://www.wjgnet.com/1007-9327/9/717.htm

INTRODUCTION

Neoadjuvant treatment is delivered as radiotherapy (RT) or radiochemotherapy (RCT) prior to surgery with the aim to devitalize primary and metastatic tumor cells and to shrink the tumor so that resection is facilitated even in case of primarily nonresectable cases[1-6]. The trials of several "neoadjuvant" radiochemotherapy have generated clear evidence downstaging is possible, resectability rates are increased, local relapse rates decreased, and survival rates possibly improved. Preoperative radiochemotherapy has been regarded as 'standard' therapy[1,7].

The infusional chemotherapy protocol of 5-FU demonstrated a higher response rate and a marginal survival benefit in advanced colorectal cancer[8]. The toxicity was lower in the infusion protocol than that in bolus protocol[9]. In chemoradiotherapy with the infusion protocol, this advantage can still work and have a theoretically better chance of drug-radiation interaction as well[10]. However, i.v. chemotherapy, either by infusion or bolus, is still a major source of discomfort to the patients.

Oral administration enables sustained exposure to 5-FU, avoids the technical barrier of intravenous (IV) administration and allows significant flexibility in choice of the dosage regimens, provided that efficacy is not compromised[11,12]. Doxifluridine (5'-deoxy-5-fluorouridine, 5'-DFuR) is synthetic 5-deoxy-nucleoside derivative. In experimental murine tumor systems, doxifluridine has achieved a therapeutic index of 10-15 times greater than that of 5-FU or other fluoropyrimidines[13]. This drug has been shown to be an effective agent when administered orally[14]. The use of oral doxifluridine and leucovorin in chemoradiotherapy provides several advantages. Administration of the drug during the entire radiotherapy course offers more chances of interaction between the drug and radiation, similar to infusion chemoradiotherapy; i.v. infusion-associated complications can be avoided. The use of oral chemotherapy also provides convenience and a comfortable environment of drug administration to patients.

In our study, 15 patients received mean dose of 41.5 Gy of pelvic irradiation with concurrent chemotherapy of 5-FU+leucovorin (LV) was administered by bolus injection during d1-3 and d26-28 of RT. 5'-DFuR were given during d4-25 of RT (RCS group). 27 similar patients treated by preoperative radiotherapy (mean dose of 42.6 Gy) were served as control (RS group). The points of the study were to evaluate the toxicity, resectability rates and relative response rates of the treatment, 3-year survival rates and 3-year recurrent rates in the two groups.

MATERIALS AND METHODS

Patients

Patients with advanced non-resectable rectal cancer were considered elegible for radiochemotherapy plus surgery study (RCS group) if they fulfilled the following criteria: Below 72 years old, KPS of 60 or over, histologically confirmed adenocarcinoma of the rectum, advanced tethered and fixed primary tumor that were considered unresectable by surgeon. From December 1995 to January 1997, 15 patients were entered in the study. They were 12 men and 3 women and age ranging from 33 to 72 years (mean 50.6). For comparison, 27 similar patients, treated by preoperative radiotherapy (40-50 Gy) plus surgery served as control (RS group). They were 21 men and 6 women and age ranging from 18 to 71 (mean 58).

Table 1 summarized the main demography and baseline characteristics of all elegible patients.The two groups were well matched for all evaluated characteristics. All tumors of

two groups were middle and lower rectal cancers (5-11cm from anus). 11 and 20 lower rectal cancers in RCS group and RS group respectively. Before starting treatment all patients underwent a general examination and got CBC done. These examinations were repeated every week during the treatment period and before operation ultrasound and/or CT or MRI and digital examination were mandatory. Digital examination was done every week.

Table 1 Patient demography and disease charateristiscs at baseline

Parameter	RCS group	RS group
Male/female	12/3	21/6
Age(years):median(range)	56(33-72)	58(18-71)
Karnofsky performance status	70-90	70-90
Primary site		
Middle	4	7
lower	11	20
Degree of differentiation		
Well	1	2
Moderate	7	15
Poor	3	4
Not specified	4	6
TNM staging		
T3N0M0	5	14
T3N1M0	0	3
T4N0M0	6	3
T4N1M0	4	5
T4N2M0	0	2

Treatment

Radiation was delivered by linear accelerator (10 MV X-ray). Similar fields were used for treatment in both groups. The initial pelvic radiation therapy volume of AP/PA ports and two lateral fields treated to 4 000 cGy. The use of a boost field to the primary tumor bed and immediately adjacent lymph nodes were given in some patients.Total doses of 4 000cGy to 4 600 cGy (mean 4 150 cGy) were delivered in 4 to 5 weeks in RCS group. Total doses of 4 000cGy to 5 000cGy (mean 4 260 cGy) were delivered in 4 to 5 weeks in RS group. In RCS group, chemotherapy was given concomitantly and consisted of two courses of 5-FU at a dose of 500 mg/m^2/day plus leucovorin at a dose of 300 mg by intravenous injection for 3 days in week 1 and week 4, 5' -DFuR was administered orally at a dose of 200 mg three times daily concomitantly during radiotherapy between interval of the two courses of intravenous chemotherapy. All patients in two groups underwent subsequent surgery 4 to 5 weeks after the preoperative treatment. 4 to 6 courses adjuvant chemotherapy (5-FU based) were given after surgery in two groups.

Evaluation of patients

Assessments of tumor dimensions and involved sites were performed before the start of treatment and were scheduled after week 4. Tumor dimensions were assessed by use of computed tomography scans, x-rays, magnetic resonance imaging. Tumor response classification was based on standard World Health Organization criteria. Disappearance of all known disease at all involved sites was considered a complete response (CR). Partial reponse (PR) was defined as residual disease with a decrease=50 % in sum of the products greatest perpendicular diameters (SPD) of all indicator lesions. Progressive disease (PD) was defined as the appearance of a

new lesion or an increase of 25 % in the SPD. Stable disease (SD) was defined as no change in SPD or a change not reaching to PR or PD. Total response rate was defined as CR plus PR. Surgical treatment results were summerized (the radical resectability rate, sphincter preservation rate and complication).

Patients were followed up every 3 months after the end of treatment with progression and survival of the disease recorded. The duration of follow-up ranged from 36-61 months (mean 43). Disease progression and survival time were analyzed according to Kaplan-Meier estimates and compared using the log-rank test. A one-sided chi-square test was used at an alpha level of 2.5 % to compare response data in two patient groups. The data of toxicity were scored retrospectively according to the World Health Organization (WHO) toxicity evaluation.

RESULTS

Tumor response

No radiochemotherapy or radiotherapy was interrupted and was then delayed because of toxicities in both groups. Obvious pain relief has been achieved in all patients of two groups presenting with buttock/sciatic/perineal pain, usually within days of commencing radiochemotherapy/radiotherapy. The median time of obvious pain relief was 7 days (range 5-10) in RCS group, 10 days (range 7-18) in RS group.

11 radical resection, 3 palliative surgery and 1 cytoreductive surgery were undertaken in RCS group.10 radical resection, 15 palliative surgery and 2 cytoreductive surgery were undertaken in RS group. Table 2 summarizes the radical resectability, sphincter preservation, lower rectal cancer sphincter preservation, response and tumor downstage rates of the two groups. Pathologic complete response (pCR) of the primary tumor was observed in two patients of RCS group.

Table 2 The radical resectability, sphincter preservation, lower rectal cancer sphincter preservation, response and tumor downstage rates in the two groups

Parameter	RCS group	RS group	P
Radical resectability rate	73.3%	37.0%	0.024
Sphincter preservation rate	26.6%	3.7%	0.028
Lower rectal cancer sphincter preservation rate	27.3%	0.0%	0.014
Response rate	46.7%	18.5%	0.053
Tumor downstage rate	53.3%	33.3%	0.206

Follow-up results

In Table 3 the 3-year overall survival rates, the disease free survival rates and the 3-year local recurrent rates are compared in the patients of two groups. Four patients of RCS group had good to excellent sphincter function.

Table 3 The 3-year overall survival, disease free survival and local recurrent rates of the patients of two groups

Parameter	RCS group	RS group	P
3-year overall survival rate	66.7%	55.6%	0.485
3-year disease free survival rate	40.1%	33.2%	0.663
3-year local recurrent rate	26.7%	48.1%	0.174

Toxicity

Patients were scored according to the WHO grading. A detailed description of acute toxicities was given in Table 4. The most relevant toxic reactions included rectal tenesmus, diarrhea and perianal area skin reaction. No toxic death was observed in

this study. No patient interrupted the radiochemotherapy and delayed the operation because of these acute toxicities. Total incidence of grade 3/4 toxicity were 73.3 % in RCS group, 44.4 % in RS group ($P=0.071$) respectively. No severe late toxicity was found in the two groups.

Table 4 WHO modified scale for acute toxicity

Site	Grading (RCS group)					Grading (RS group)				
	0	1	2	3	4	0	1	2	3	4
Hematologic:										
Neutropenia	8	2	4	1	0	19	3	5	0	0
Non-hematologic:										
Small bowl	4	3	7	3	0	6	9	10	2	0
Bladder	6	4	5	0	0	10	11	6	0	0
Skin	0	2	6	7	0	0	10	8	9	0

DISCUSSION

Preoperative radiotherapy (RT) (45 Gy) with continuous infusion of 5-FU for 5 days per week with or without CDDP were used by the M.D. Anderson group[15] in locally advanced tethered and fixed primary rectal cancer to downstage the tumors. It was concluded that preoperative radiochemotherapy decreased the local recurrence rate as compared to preoperative radiotherapy only, with no increase of surgical morbidity and late morbidity after a follow-up of 3 years. In this study, the acute toxicities of grade 3 in RCS group were more pronounced than that in RS group but without statistical differences and no patient had interrupted the radiochemotherapy and delayed the operation because of these acute toxicities. University of Uppsala study[16] proved that the volume of bowel under radiation, rather than the energy of the radiation influence postoperative mortality, and emphasize the importance of precise radiotherapy planning to minimize normal tissue toxic reactions.

Continuous infusion of 5-FU led to significantly higher response rates than bolus 5-FU, and a meta-analysis identified a statistically significant increase in overall survival[17]. However, this improvement was the only report, and other trials had failed to repeat the significant survival benefit. Continuous infusion 5-FU is not routinely practised, partly because of its inconvenience and cost and partly due to central venous access that might cause significant complications in 15 % to 20 % of patients[18], including infections, bleeding, thrombosis, and pneumothorax. Each of these complications has a negative impact on quality of life. Several of the new chemotherapy drugs used in colorectal cancer also appear to be radiosensitizers. Pilot and phase II trials incorporating irinotecan and oxaliplatin[19] into 5-FU-plus-radiation program are currently used, with encouraging results. Similarly, the oral 5-FU prodrugs[20,21] represent promising new agents to combine with radiation. The oral route not only makes these drugs convenient to the patient but also gives prolonged theraputic serum levels, simulating continuous venous infusion, which may be the preferable fluoropyrimidine schedule for radiosensitization.

5-FU as a radiosensitizer was given by continuous infusion. 5'-DFuR kills cancer cell through PyNPase transformation. The study by Watanabe *et al*[22] found that fifty three patients with advanced colorectal cancer when given single oral doses of 5'-DFuR, high 5-FU concentration and PyNPase activity were noted in tumor tissue and lymph nodes. Effective 5-FU concentration in tumor tissue was maintained even 24 hours after treatment. Effective lymph node concentration of 5-FU was maintained even 8 hours after treatment. PyNPase activity in tumor tissue was significantly higher than that in the normal

intestinal mucosa ($P<0.05$). In this study, pre-operative radiochemotherapy was well tolerated. The relatively hight rate of curative resections indicates that 5-FU and Oral 5'-DFuR treatment as radiosensizers, maintaining highier concentrations of 5-FU during RT, are safe and effective. The aim of giving two courses of 5-FU intravenous injection was to relieve the local symptoms of the patients with local advanced rectal cancer and to improve systemic treatment efficacy. The appropriate dosage of oral 5'-DFuR as radiosensitizer during RT should be further studied.

Sphincter preservation rate and sphincter preservation rate of lower rectal cancer in RCS group were significantly higher than that of RS group. Therefore, this study at least demonstrates that sphincter preservation operation did not decrease local control and survival rates, although when local control and survival rates were analyzed, the RCS group had no significant advantage compared with RS group. But it is very important to meet the request of sphincter preservation by the rectal cancer patients and to improve their quality of life.

Local failure rates are high for locally irresectable primary or recurrent colorectal cancer, even when chemoradiation therapy is employed. A tumor-free surgical resection margins are paramount to achieve cure[23-25]. In this study, the radical resectability rate in the RCS group was significantly higher than that in RS group, but without significant decrease local relapse rate, and no significant improvement of survival rate. Therefore, further study of this modality of treatment should be continued[26-32].

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Edited by Xu JY