World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i27.3229

World J Gastroenterol 2011 July 21; 17(27): 3229-3234
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Oncologic outcomes of primary and post-irradiated early stage rectal cancer: A retrospective cohort study

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Received: November 1, 2010 Revised: December 5, 2010
Accepted: December 12, 2010
Published online: July 21, 2011

Abstract

AIM: To evaluate the oncologic outcomes of primary and post-irradiated early stage rectal cancer and the effectiveness of adjuvant chemotherapy for rectal cancer patients.

METHODS: Eighty-four patients with stage I rectal cancer after radical surgery were studied retrospectively and divided into ypstage I group (n = 45) and pstage I group (n = 39), according to their preoperative radiation, and compared by univariate and multivariate analysis.

RESULTS: The median follow-up time of patients was 70 mo. No significant difference was observed in disease progression between the two groups. The 5-year disease-free survival rate was 84.4% and 92.3%, respectively (P = 0.327) and the 5-year overall survival rate was 88.9% and 92.3%, respectively, for the two groups (P = 0.692). The disease progression was not significantly associated with the pretreatment clinical stage in ypstage I group. The 5-year disease progression rate was 10.5% and 19.2%, respectively, for the patients who received adjuvant chemotherapy and for those who rejected chemotherapy in the ypstage I group (P = 0.681).

CONCLUSION: The oncologic outcomes of primary and post-irradiated early stage rectal cancer are similar. Patients with ypstage I rectal cancer may slightly benefit from adjuvant chemotherapy.

Key words: Rectal cancer; Neoadjuvant radiotherapy; Total mesorectal excision

Peer reviewer: Omar Vergara-Fernandez, MD, Departments of Surgery, National Institute for Medical Sciences and Nutrition Salvador Zubirán, Vasco de Quiroga No. 15, Col. Seccion XVI. Deleg. Tlalpan, CP 14000, Mexico

Du CZ, Chen YC, Cai Y, Xue WC, Gu J. Oncologic outcomes of primary and post-irradiated early stage rectal cancer: A retrospective cohort study. *World J Gastroenterol* 2011; 17(27): 3229-3234 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i27/3229.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i27.3229

INTRODUCTION

Rectal cancer is a worldwide health concern[1,2]. It is the fifth leading cause of cancer-related death and its incidence is increasing at a rate of 4.2% per year in China[2].

Currently, the management of rectal cancer has become multidisciplinary[3-5]. Neoadjuvant therapy, including long- or short-course chemo- and radiotherapy, can control locally advanced rectal cancer and increase the sphincter preservation rate[6-8].

Neoadjuvant therapy can decrease the tumor size and histopathological stage in a considerable number of rectal cancer patients, depending on the dose of radiation, chemotherapy regimen, and many other factors[9-12]. The pathologic stage of tumor after neoadjuvant therapy (ypstage) is one of the most important factors for oncologic outcome, and the clinical and pathologic meanings of ypstage are different from those of primary pathologic TNM stage (pstage)[13,14]. For example, patients with early stage rectal cancer (pT1-2N0M0) have a low risk of progression and no indication for adjuvant chemotherapy. Nevertheless, patients with ypstage I rectal cancer should undergo postoperative chemotherapy according to the National comprehensive cancer network guidelines[15], since some studies suggested that adjuvant chemotherapy may further decrease the risk of rectal cancer progression in patients who have received preoperative radiation[13-16]. However, to date, no worldwide consensus has been reached on whether adjuvant chemotherapy is proper for patients with ypstage I rectal cancer. Few studies have neither specifically compared the prognostic difference in ypstage I and pstage I rectal cancer, nor investigated the effectiveness of adjuvant chemotherapy for post-irradiated early stage rectal cancer. Thus, this study was to compare the long-term outcomes of ypstage I and pstage I rectal cancer patients after radical resection, and the outcomes of ypstage I patients who received post-operative chemotherapy with those who did not receive chemotherapy.

MATERIALS AND METHODS

Data were collected from all patients with pathologic stage I rectal cancer admitted to Peking University Cancer Hospital from February 1998 to February 2005. The inclusion criteria were those with histologically identified primary adenocarcinoma of the rectum before treatment, resectable rectal cancer 12 cm or less from the anal verge, evaluated by endorectal ultrasound (ERUS) or magnetic resonance imaging (MRI) before treatment, no clinical evidence of synchronous distant metastases, transabdominal radical resection based on the principle of total mesorectal excision (TME), and R0 resection.

The exclusion criteria were those with transanal excision, pathologic complete response to neoadjuvant radiotherapy, multiple primary malignancy or history of other malignant tumors within 5 years, familial adenomatous polyposis and hereditary non-polyposis colorectal carcinoma, and those who died of complications or due to other non-cancer related reasons.

Finally, 84 eligible patients were included in this study and divided into ypstage I group (n = 45) and pstage I group (n = 39). Demographic and clinical data of the patients are presented in Table 1.

Table 1 Characteristics of patients included in this study

Characteristic	Group		*P* value
	Ypstage I (n = 45)	Pstage I (n = 39)	
Gender			
Male	28	21	0.437
Female	17	18	
Age (yr)			
< 60	19	10	0.111
> 60	26	29	
Median	62	67	
Distance from anal verge (cm)			
≤ 5	20	9	0.040
> 5	25	30	
Pretreatment serum CEA (ng/mL)			
≤ 5	29	32	0.016
> 5	13	3	
unknown	3	4	
Surgery			
APR	14	6	0.091
LAR	31	33	
Clinical and pathologic stage			
cT1-2N0	0	28	< 0.001
cT3-4N0	15	6	
cTanyN+	30	5	
pT1N0	5	14	0.007
pT2N0	40	25	
Histological differentiation			
High	3	15	< 0.001
Moderate	34	23	
Poor	8	1	
Lymphovascular invasion			
Positive	0	1	0.464
Negative	45	38	
NELN			
< 12	27	23	0.924
≥ 12	18	16	

APR: Abdominoperineal resection; LAR: Low anterior resection; NELN: Number of examined lymph nodes; CEA: Carcinoembryonic antigen.

Neoadjuvant radiotherapy

Neoadjuvant radiotherapy was indicated for patients with clinical T stage more than T2 (T3 or T4), or with nodes involved. We adopted the regimen recommended by the Chinese Anti-Cancer Association[17]. The patients were irradiated with a 10 MV dual photon linear accelerator using a 3-field box technique (posteroanterior and bilateral fields). The total radiation dosage was 3000 cGy in 10 fractions delivered within 2 wk, with a biological equivalent dose of 36 Gy. The radiation field was set at the upper margin 1.5 cm above the sacral promontory (L5 level), bilateral margin 1 cm outside the pelvic brim, and inferior margin 3 cm below the lower margin of the tumor, or at the anal verge in some lower rectal cancer cases. Surgery was performed 2-3 wk after radiotherapy.

Surgery

All included patients underwent radical resection according to the TME principles[18], irrespective as to whether they received abdominoperineal resection or low anterior resection. All surgeries were performed by sharp pelvic dissection under direct vision along the Holly plane. The

mesorectum was excised 4-5 cm from the distal inferior edge of upper rectal cancer, and TME was performed in mid-level and lower rectal cancer. The bowel wall was excised at least 2 cm from the distal inferior edge of the tumor. All surgeries were performed by the same surgeon. R0 resection was defined when no microscopic residual tumor cells were found at the distal and circumferential resection margins.

Pathologic evaluation

Pathologic evaluation was performed again by one senior pathologist who was blinded to the clinical and oncologic outcome of the patients. All resected specimens were stained with hematoxylin and eosin, and evaluated for tumor differentiation and invasion, lymph node metastases, and lymphovascular invasion (LVI). The pathologic stage of rectal cancer was evaluated according to the 6th UICC TNM Staging System after histopathological examination.

Adjuvant chemotherapy

Of the 45 patients in the ypstage I group who were recommended to receive postoperative chemotherapy, 19 accepted chemotherapy and 26 refused adjuvant chemotherapy because of lack of authoritative evidence and consensus in China. The patients underwent adjuvant chemotherapy with 5-FU or capecitabine in combination with FOLFOX and CapeOX or capecitabine alone, according to their condition for 8-12 cycles. Patients in the pstage I group had no indications for chemotherapy, and were thus observed after surgery with a regular follow-up.

Follow-up

All patients were followed up every 3 mo during the first 2 years after surgery, and then every 6 mo for 5 years. Clinical examination was performed and serum Carcinoembryonic antigen (CEA) was detected at each follow-up. Abdominal ultrasound, pelvic MRI, and chest radiograph were performed every 6 mo, and colonoscopy was performed annually. The follow-up time was 3-131 mo (mean 70 mo). The terminal time for evaluation of outcomes was 5 years. The follow-up rate was 89.3% with 9 inconclusive results (follow-up was lost in 2 patients after disease progression).

Statistical analysis

Statistical analysis was performed using SPSS 16.0 statistical software (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed by Pearson chi-squared or Fisher's exact test when appropriate. Kaplan-Meier survival curve was used to estimate the number of patients surviving or remaining disease-free at each time. Disease-free survival (DFS) and overall survival (OS) curves were compared between the two groups using the Wilcoxon test for time-to-event parameters. Multivariate Cox proportional hazards regression (forward stepwise selection) was used to analyze the major factors affecting DFS rate. All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant.

Table 2 Oncologic outcomes of patients in two groups *n* (%)

	Ypstage I	Pstage I	*P* value
Local recurrence rate	2 (4.4)	1 (2.6)	1.000[1]
Distant metastasis rate	6 (13.3)	3 (7.7)	0.494[1]
5-yr DFS rate	38 (84.4)	36 (92.3)	0.327
5-yr OS rate	40 (88.9)	36 (92.3)	0.692

[1]Fisher's exact test. DFS: Disease free survival; OS: Overall survival.

Table 3 Correlation between clinical stage and disease progression in ypstage I group

Clinical stage	Disease progression (*n*)		OR (95% CI)	*P* value
	Yes	No		
cT3-4N0	3	12	0.31-8.43	0.670[1]
cTanyN+	4	26		

[1]Fisher's exact test. OR: Odds ratio.

RESULTS

Characteristics of patients

Eighty-four patients (49 males and 35 females) were included in this study with a median age of 64 years (range, 28-80 years). Complete follow-up information about the patients was available except for 9 patients (5 in ypstage I group and 4 in pstage I group) after surgery. No statistically significant difference was observed in gender and age of the patients, surgery, number of examined lymph nodes and LVI between the two groups (Table 1). However, a significant difference was found in distal anal verge (DAV), preoperative serum CEA level, histological differentiation, and pathologic T stage between the two groups, indicating that the condition of patients is better in pstage I group than in ypstage I group (Table 1).

Disease progression

Local recurrence was noted in 3 patients (3.6%). The 5-year local recurrence rate was 4.4% in ypstage I group and 2.6% in pstage I group (Table 2). Distant metastasis was observed in 9 patients (10.7%), which initially occurred in the liver of 5 patients (55.6%), in the lung of 3 patients (33.3%), and in the ovary of 1 patient (11.1%). The 5-year distant metastasis rate was 13.3% in ypstage I group and 7.7% in pstage I group (Table 2).

Disease progression was observed in 7 patients of the ypstage I group. Of the 7 patients, 4 had lymph node involvement based on ERUS/MRI before treatment and 3 were staged as T3-4N0. Pretreatment clinical stage was not significantly associated with disease progression in ypstage I group [odds ratio (OR) = 0.31-8.43, $P = 0.670$, Table 3].

Five-year DFS and 5-year OS rate

The overall 5-year DFS and 5-year OS rate was 88.1%, and 90.5%, respectively for the two groups. The 5-year DFS rate was 84.4% and 92.3%, respectively ($P = 0.327$,

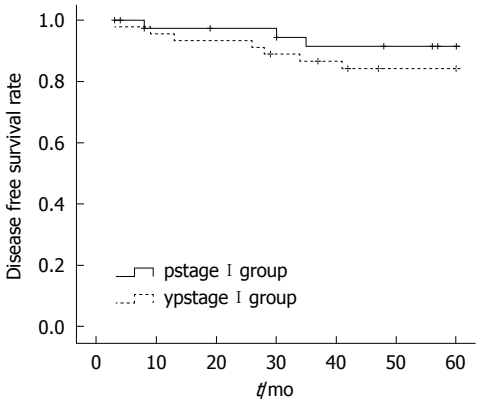

Figure 1 Five-year disease-free survival rate for patients in two groups.

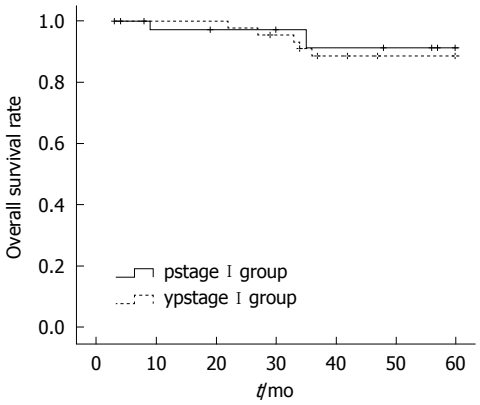

Figure 2 Five-year overall survival rate for patients in two groups.

Figure 1, Table 2) while the 5-year OS rate was 88.9% and 92.3%, respectively ($P = 0.692$, Figure 2, Table 2) for the two groups.

Effectiveness of chemotherapy for ypstage I patients

Of the 45 patients in ypstage I group, 19 received adjuvant chemotherapy and 26 rejected chemotherapy. The 5-year disease progression rate was 10.5% and 19.2%, respectively, for the patients who accepted chemotherapy and those who rejected chemotherapy (OR = 0.09-2.87, $P = 0.681$, Table 4).

Prognostic factors affecting DFS rate

Multivariate analysis demonstrated that the pretreatment serum CEA level was the major factor affecting the 5-year DFS rate for early stage rectal cancer patients (Table 5). Gender, age, neoadjuvant radiotherapy, DAV, histological differentiation, pathologic T stage, lymph nodes, LVI, and adjuvant chemotherapy were not the independent factors for the long-term DFS rate.

DISCUSSION

Currently, multidisciplinary management of advanced rectal cancer has gained wide acceptance[3-5]. Neoadjuvant radiotherapy is an effective treatment modality for locally advanced rectal cancer with respect to resectability, local control, and survival benefit[19-21]. The tumor stage decreases in approximately 40%-60% of rectal cancer patients obtain after neoadjuvant radiotherapy, which is related to a long-term favorable oncologic outcome[11,13,22]. One fifth of patients with ypstage I rectal cancer can directly benefit from neoadjuvant therapy[23,24]. Although it is widely acknowledged that ypTNM stage and primary TNM stage are different in terms of clinical meaning[9,25,26], few studies have specially compared the difference in early stage rectal cancer between post-irradiated patients and those undergoing direct surgery. In this study, patients with early stage rectal cancer were selected to undergo radical surgery instead of transanal local resection as a control in order to enhance the comparability of the two arms.

In the present study, the pstage I rectal cancer patients undergoing radical surgery had a favorable outcome, with a 5-year disease progression rate of < 10% and an OS rate of > 90%, which is consistent with the reported data[27,28]. Compared the patients in pstage I group, those in ypstage I group had several potential risk factors for poor oncologic outcomes, such as higher CEA level, more advanced T stage, and poorer histological differentiation, which is consistent with the reported data[29,30]. However, the patients in ypstage I group did not exhibit a higher disease progression rate or cancer-related death than those in pstage I group. Multivariate analysis also revealed that only serum CEA level was the major factor affecting DFS rate for early stage rectal cancer patients. Reerink *et al*[25] also showed that the prognosis of of patients with initially unresectable rectal tumor down-staged to pT2 and those

Table 4 Correlation between adjuvant chemotherapy and disease progression in ypstage I group

Adjuvant chemotherapy	Disease progression (*n*)		OR (95% CI)	*P* value
	Yes	No		
Yes	2	17	0.09-2.87	0.681[1]
No	5	21		

[1]Fisher's exact test. OR: Odds ratio.

Table 5 Multivariate analysis of disease-free survival rate by COX model (forward method)

Variable	Hazard ratio	95% CI	*P* value
Pretreatment serum CEA	5.535	1.574-19.468	0.008
Distance from anal verge	0.715	0.453-1.130	0.064
Gender	0.483	0.174-1.337	0.154
Age	1.057	0.999-1.119	0.054
Neoadjuvant radiotherapy	0.490	0.176-1.362	0.244
Histological differentiation	1.161	0.452-2.980	0.929
Pathologic T stage	0.827	0.232-0.953	0.271
Lymphovascular invasion	1.643	0.164-16.480	0.829
NELN	0.946	0.880-1.017	0.244
Adjuvant chemotherapy	1.381	0.512-3.725	0.670

NELN: Number of examined lymph nodes; CEA: Carcinoembryonic antigen.

with primary resectable cancer with the same T classification is similar. Our study further demonstrated that post-irradiated early stage rectal cancer has no significant heterogeneity in prognosis compared to primary early stage rectal cancer.

Up to date, no general agreement has been reached on the indications of adjuvant chemotherapy for post-irradiated patients. Short-course radiation is predominantly used in European countries, although no consensus has been reached. Most doctors believe that postoperative pathologic stage of rectal cancer is still the decisive factor for adjuvant chemotherapy, since its down-staging rate is less than 1%[31]. The role of adjuvant chemotherapy in down-staged patients after preoperative long-course radiation is controversial. It has been demonstrated that chemotherapy, whether preoperative or postoperative, reduces the overall risk of disease progression in patients undergoing neoadjuvant radiotherapy[16]. However, which patients would benefit from adjuvant chemotherapy needs to further investigated[32]. Fietkau *et al*[33] reported that postoperative chemotherapy is not necessary for patients with ypN0 after neoadjuvant chemo- and radiotherapy because no obvious improvement has been achieved in 3-year DFS rate. Collette *et al*[13] suggested that patients with down-staged ypT0-2, irrespective of ypN status, can benefit from adjuvant chemotherapy. No consensus has been reached on the indications of chemotherapy for post-irradiated patients in China. The results of this study suggest that adjuvant chemotherapy may be beneficial for the patients with ypT1-2N0 after neoadjuvant radiotherapy alone, since its outcome is better in patients after chemotherapy. Although the difference in disease progression rate did not show statistical significance, this two-fold difference is of clinical significance. Moreover, the results were largely influenced by the small sample size of patients in this study, thus further randomized study with a large sample size is needed.

In conclusion, the oncologic outcome of primary and post irradiated early stage rectal cancer after neoadjuvant radiotherapy is similar. Furthermore, patients with ypstage I rectal cancer may slightly benefit from adjuvant chemotherapy.

ACKNOWLEDGMENTS

The authors appreciate Dr. Abraham KC Ho in Peking University Health Center for his great effort on this study.

COMMENTS

Background

Currently, neoadjuvant radiotherapy has been regarded as an effective treatment modality for locally advanced rectal cancer in terms of improving its local control and increasing the sphincter preservation rate. The pathologic stage of rectal cancer after neoadjuvant therapy (ypstage) is one of the most important factors affecting its oncologic outcome, and the clinical and pathologic meanings of ypstage are different from those of primary pathologic TNM stage (pstage). However, few studies have specially investigated the prognosis of post-irradiated early stage rectal cancer patients. Thus, this study was conducted to compare the long-term outcomes of ypstage I and pstage I rectal cancer patients after radical resection, and the outcomes of ypstage I patients who received postoperative chemotherapy with those who did not receive chemotherapy.

Research frontiers

This study specially addressed the long-term oncologic outcome of post-irradiated early stage rectal cancer by well-designed cohort study.

Innovations and breakthroughs

This study demonstrated that the oncologic outcome of primary and post-irradiated early stage rectal cancer was similar. Furthermore, patients with ypstage I rectal cancer may slightly benefit from adjuvant chemotherapy.

Applications

The post-irradiated early stage rectal cancer has a good oncologic outcome, and the clinical value of postoperative adjuvant chemotherapy should be further studied with a large sample size.

Peer review

This retrospective study comparing the ypstage I and pstage I rectal cancer patients after radical resection demonstrated that down-staging of rectal cancer was related to a long-term favorable oncologic outcome (5-year local recurrence rate, disease-free and overall survival rate). Pretreatment serum Carcinoembryonic antigen level was the major factor affecting the 5-year disease-free survival rate. On the other hand, it showed that patients with ypstage I rectal cancer could benefit from adjuvant chemotherapy.

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S- Editor Tian L **L- Editor** Wang XL **E- Editor** Zheng XM