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Original Article

Effect of concurrent radiotherapy and simultaneous oral capecitabine chemotherapy on locally advanced middle and lower rectal cancer

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Abstract: Objective: To assess the safety and efficacy of preoperative intensity-modulated radiotherapy (IMRT) with oral capecitabine in patients with locally advanced mid-low rectal cancer using a simultaneous integrated boost (SIB) of tomotherapy. Methods: Between 2012 and 2014, total Sixteen Patients with resectable locally advanced mid-low rectal cancer patients with T3 to T4 and/or N+ rectal cancer were eligible. The eligible patients received IMRT to 2 dose levels simultaneously 55 and 47.5 Gy in 25 fractions with concurrent capecitabine 825 mg/m^2 twice daily 5 days/week. Total mesorectal excision (TME) was performed 6-9 week after the completion of chemoradiation. The primary end point included toxicity, rate of sphincter-sparing, postoperative complication, and pathological complete response rate (pCR). Result: All patients completed chemoradiation without any treatment break. Tomotherapy showed superiority with respect to target coverage, homogeneity, and conformality 2 patients refused radical surgery because of almost complete primary tumor regression and complete symptom relief after neoadjuvant therapy. Fourteen patients underwent surgical resection and eleven patients 78.6% underwent sphincter-sparing lower anterior resection. 4 patients 28.6% had a pathological complete response (pCR). The incidence of grade 1-2 hematologic, gastro-intestinal toxicities was 62.5% (10/16) and 18.8% (3/16). The incidence of grade 3 skin toxicities were 68.8% (10/16). Grade 4 toxicity was not observed. Surgical complications incisional infection on thirteen after surgery was observed in 1 patients. Conclusion: Preoperative simultaneous integrated boost (SIB) of tomotherapy with concurrent oral capecitabine is safe and well tolerated in patients in a promising local control. However, a larger number of patients and a long follow-up are required to assess its potential superiority.

Keywords: Rectal neoplasms, tomotherapy, simultaneous integrated boost, capecitabine

Introduction

In 1994, the Paris Conference suggested that since rectal cancer adopted preoperative radiotherapy and chemotherapy combined with neoadjuvant therapy, neoadjuvant therapy of rectal cancer has reduced tumor clinical stages, and improved radical resection rate of middle and late stage of rectal cancer and retention rate on middle and low of rectal cancer, its side effects can be tolerated. Currently, for resectable locally advanced middle and lower rectal cancer, preoperative concurrent radiotherapy and chemotherapy united with total TME mesorectal excision (TME) has become the standard treatment program. The dose of radiotherapy is very important for the tumor. In the dose range of 40~60 Gy, the effect on rectal cancer has been obvious-a local irradiation dose of rectal tumor and clinical and pathological complete remission (PCR). After improving the prognosis, unnecessary surgery shall be avoided in selective cases [1-4]. Recently, some rectal cancer has emphasized IMRT research shows that compared with traditional field irradiation and three-dimensional conformal radiotherapy, IMRT can reduce the organ at risk OAR dose and improve the local dose of tumor without causing side effects upon the gastrointestinal tract and urinary system [5, 6]. Spiral fault radiotherapy is an image inducing IMRT technology. Most conventional IMRT can obtain better dose distribution of target coverage, at uniform and conformal degrees [7-9]. The research adopts spiral fault concurrent radiotherapy (SIB-IMRT), and discusses the simulta-

Table 1. Characteristics of the studied patients

Case number	N (%)
Age (years) median 53.0 (range, 34-72)	
Gender	
Male	11 (68.8)
Female	5 (31.2)
Distance from anal verge	
≤5 cm	12 (75.0)
>5 cm	4 (25.0)
Clinical tumor stage (T)	
T3	15 (94.8)
T4 (T4a+T4b)	1 (5.2)
Initial nodal stage (N)	
N0	6 (37.5)
N1	7 (44.8)
N2	3 (18.7)
Tumor differentiation	
Well	1 (6.2)
Moderate	14 (87.6)
Poorly	1 (6.2)
Uncertain type	0 (0.0)

neous addition of rectal primary foci and metastatic lymph nodes. Under the premise of not prolonging radiation time, to synchronously oral capecitabine chemotherapy for sensibilization, to increase PCR rate and observe the safety and feasibility. There are 16 cases in the group. The preliminary results are as follows.

Materials and methods

General materials

Select 16 cases of patients with locally advanced middle and lower rectal cancer accepting preoperative concurrent radiotherapy and synchronously oral capecitabine chemotherapy operated in our hospital from Sept, 2012 to Aug, 2014.

Entry criteria: Passed fiber rectum microscopic pathology, they are verified as rectum adenocarcinoma; Pelvic MRI check mentioned that TNM stages are divided into II and III periods; KPS score is 80~100; abdominal cavity not confirmed by imaging appears distant metastasis; no chemotherapy and history of abdominal radiotherapy. Among 16 cases of patients, there are 11 male patients and 5 female patients; the age is 34~72, with a middle age of 53 years old. There are 10 cases of adenocarcinoma, 3 cases of mucinous cell carcinoma, 2 cases of ring cell carcinoma, and 1 case unclassified. Tumor margin distance to the anus is 3~8 cm, with a middle distance of 4 cm. Specific parameters see **Table 1**.

Therapy method

CT simulation location: Patients are fasting. After bladder filling, the patients are in supine or prone position. When fixing hydrolysis thermoplastic film body cover, before 90 minutes and 40 minutes of Philips CT scanning, orally use 2% meglucamine diatrizoate of 600 mL for each, to show the small intestine and intravenous iodine alcohol of 100 ml to strengthen the scanning. The scanning scope is from second lower edge of the lumbar vertebra to 1/3 of femur. The scanning thickness is 5 mm. Upload the image to the tomotherapy system through the LAN.

Design of target area and treatment plan: The target area is delineated with reference to No. ICRU 50 and 60 reports. Positioning of CT image is combined with MRI, and rectum mirror, rectum inner ultra-sound and rectum check to confirm gross target volume GTV; pGTV (planning GTV) is GTV placed 8 mm outside; clinical target volume (CTV) refers to rectum membrane district, internal iliac, external iliac lymph drainage area, presacral region, obturator lymph nodes, total rectum, the sciatic rectum fossa and anal canal; planning target volume (PTV) is GTV placed 3 mm outside. OAR includes small intestine, bladder, femoral head and pelvis within the PTV upper edge for 1 cm. OAR dose: small intestine Dmax<54 Gy, V50≤5%, V40≤30%, V30≤50%, V15≤150 ml; Bladder average dose ≤21 Gy, V40<50%; caput femurs V30<15%. Field width of tomotherapy is 2.5 cm, with a modulation factor of 2.8~3.0.

Prescription dose and registration: Before daily treatment, adopt MVCT to scan the target district, and obtain the image and original positioning CT image based upon the registration of anatomical structure of sacrococcyx, so as to correct the position error. PTV provides 47.5 Gy/25 fractions, 1.9 Gy/fractions, pGTV add the amount to the same period of 55 Gy/25 fractions, 2.2 Gy/fractions. Radiotherapy process is 5 weeks, 5 d/weeks, 1 fraction/d.

Chemotherapy and operation: Oral administration from first days after radiotherapy for

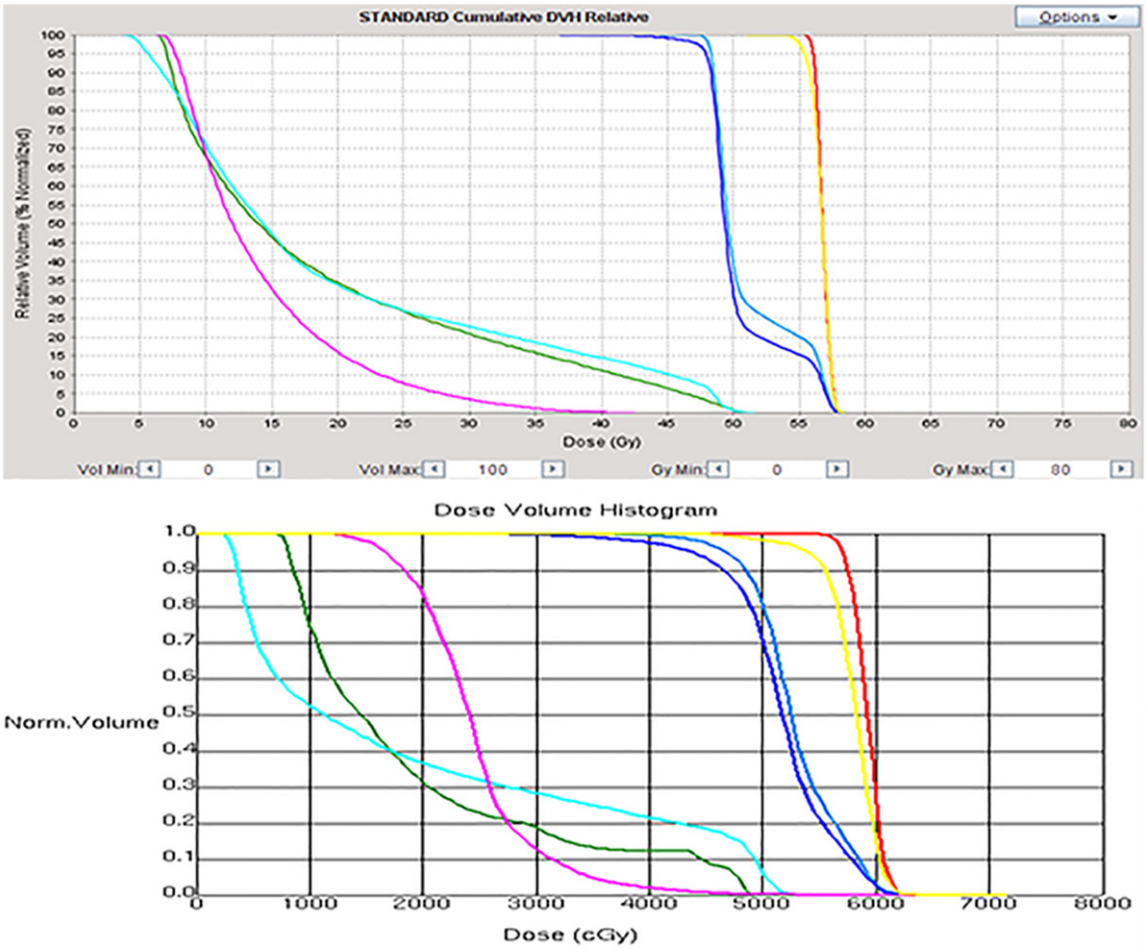

Figure 1. 44-year male low rectal cancer patient (cT3N0M0). A. TOMO planning, B. Traditional IMRT planning. Red: GTV, yellow: pGTV, lightblue: CTV, blue: PTV, skyblue: small bowel, forest: colon, purple: femoral head.

Table 2. Acute toxicities and perioperative complications in patients with locally advanced mid-low rectal cancer

Acute toxicities	N = 16 (%)
Diarrhea	
Grade 1	3 (18.8)
Leukopenia	
Grade 1	7 (43.7)
Grade 2	3 (18.8)
Dermatitis	
Grade 1	1 (6.0)
Grade 2	5 (31.2)
Grade 3	10 (68.8)
Perioperative complications	N = 14 (%)
Anastomotic infection (after low anterior resection)	1 (6.0)

capecitabine, 825 mg/m^2 for each fraction, 2 fractions/d, 5 d/weeks, for a total of 5 weeks. Oral administration was no longer given after radiotherapy for capecitabine or other chemotherapy. After chemotherapy is finished for 8~9 weeks, operate TME, with the operation mode of combined abdominal perineal resection (APR) or rectal cancer lower anterior resection (LAR).

Side effect evaluation

During the period of chemotherapy for all the patients, operate blood routines, blood biochemistry and liver function test every week. Adverse reactions to chemotherapy shall be classified according to NCI-CTC3.0 standard [10].

Result

Tomotherapy dose distribution and dose volume

Prescription dose covers at least 96% of the target area. pGTV and PTV dose distribution are

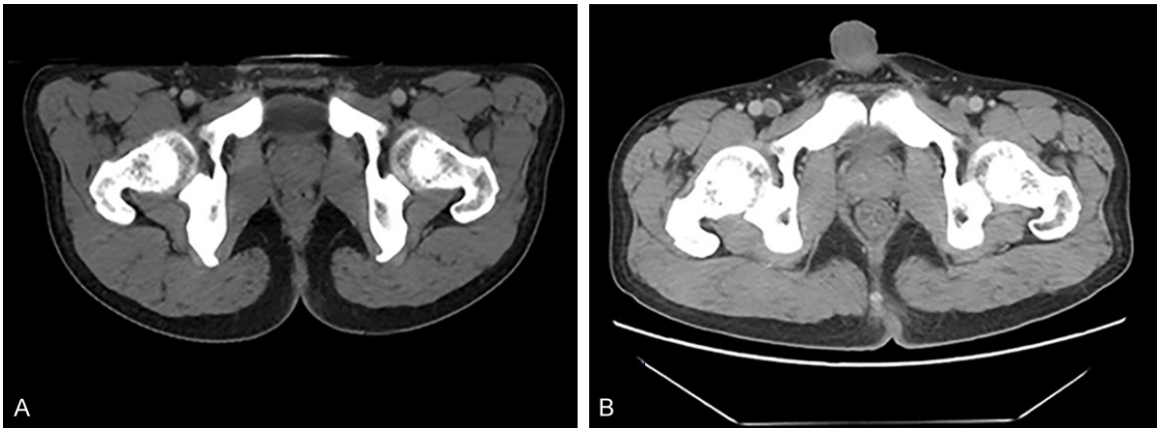

Figure 2. (A) CT before chemo-radiotherapy and (B) CT of 6 months after sphincter-sparing lower anterior resection.

uniform, and accept ≤107% of the prescription dose at 1% of any PTV volume. The dose of endangered organs is low, to reach the limitation standard. Compared with conventional static intensity modulated radiotherapy plans, tomotherapy radiotherapy obtained better target district covering, with uniformity and conformal dose distribution (see **Figure 1**).

Chemotherapy complete situation and acute adverse reactions

All the 16 cases of patients completed simultaneous chemotherapy, and accepted a radiotherapy dose. The adverse reaction rate of I and II degree of blood system (white blood cells or platelets) is 62.5% (10/16), among them, 7 cases are I degree, and 3 cases are II degree. The incidence of gastrointestinal reactions was 18.8% (3/16), of I degree diarrhea. The incidence of toxic and side effects of skin damage in the area of the anus and perineal region was 100% (16/16); among which, 6 cases are I and II degree (31.2%) (6/16), and 10 cases are III degree (68.8%). No toxic side effects occurred above IV degree, and no serious adverse effects resulted in chemotherapy interruption or dose adjustment (**Table 2**).

Recent curative effect

All the patients underwent a preoperative rectum check and rectum mirror check. 6 cases reached the clinical PCR, and among them 2 patients refused to accept the operation any further, and disease-free survival followed up for 7 months and 13 months respectively. 11 cases out of 14 cases of operation patients (78.6%) underwent a rectum lower anterior resection of anus (**Figure 2**). 3 cases underwent an abdominal perineal jointed with rectal cancer operation, and the tumor complete resection rate (R0 resection rate) is 100%. 1 patient was operated upon with wound infection, without perioperative death. The pathological response evaluation of 14 patients are: 28.6% (4/14) and reached PCR after the operation. The total declining rate of clinical T and N stages are 71.4% (11/14), and among them the declining period of T is 78.6% (10/14), and N's declining period is 71.4% (5/7). The operation retention rate is 71.4% (10/14).

Discussion

There are quite a lot of disputes about the optimal treatment method for rectal cancer.

Although preoperative and postoperative radiotherapy are effective, recent trends are more likely to be neoadjuvant therapy, especially the joint chemotherapy neoadjuvant therapy [11]. During the tumor's declining period, the removal rate is increased, and the scope of anus preservation in potential remote rectal cancer can stimulate the application of neoadjuvant therapy in rectal cancer.

Recently, the new chemotherapy drugs include Oxaliplatin, irinotecan and S-1 for the preoperative concurrent radiotherapy, regardless of single or two joint and (or) 5-Fu (5 Fluorouracil) united drug, there is no indication to be prior to the single application of 5-Fu injection or PCR rate of oral capecitabine [12-14]. Capecitabine is one kind of orally administered drug, which is

absorbed into the gastrointestinal tract, and can simulate the effect of continuing to inject 5-Fu, to avoid side effects and complications caused by central venous transfusion of 5-Fu [15]. Capecitabine can be transferred from thymidine phosphate (TP) inside the cell into active 5-Fu, and the concentration of TP is relatively high in the tumor cell, especially the rectum tumor, compared with vein injection of 5-Fu, to form the advantage of capecitabine in the therapy [16]. The research shows that capecitabine together with radiotherapy is similar with the effect of 5-Fu. Therefore, the drug has a bright future in neoadjuvant therapy experiments [17, 18]. Capecitabine is usually prescribed twice. During the whole process of radiotherapy, it is used twice per day, at 825 mg/m^2 for each time. Compared with 5-Fu/calcium folinate, acute toxicity of capecitabine is relatively little, such as diarrhea, stomatitis, nausea and neutropenia, plus with easy and feasible oral capecitabine, so the research adopted the chemotherapy plan of using oral capecitabine.

Several earlier researchers have shown the impact of increasing radiotherapy dose amount in neoadjuvant therapy on PCR [1, 2], which indicates that PCR has extremely important prognosis value toward partial middle and late stage of rectal cancer after neoadjuvant therapy. The increasing rate of PCR predicts the increasing rate of partial control rate, no disaster survival rate (DFS) and total survival rate (OS) [19, 20]. Capicri *et al.* [19] visited 566 cases of patients with partial middle and late stage rectal cancer after neoadjuvant therapy, with local recurrence rate and distant metastasis rate of PCR patients at only 1.6% and 8.9%. DFS and OS for 5 years were 85% and 90% separately. The summary analysis result proposed by Zorcolo *et al.* [20] shows that PCR improved DFS and OS for 5 years obviously compared with the PCR reaching group. Ballonoff *et al.* [21] launched clinical research for II period, and the patients with removal partial middle and late stage of rectal cancer adopted SIB-IMRT technology with pelvic 45 Gy/25 fractions. Primary tumor and metastatic lymph nodes are provided with an additional amount of the same period to 55 Gy/25 fractions, and oral capecitabine, synchronized with chemotherapy. Postoperative pathology shows that the PCR rate is 38%, and adverse incidence of acute phase of level 3 and 4 is 13%. The research obtained the maximum PCR rate for the clinical experiment rate of rectal cancer neoadjuvant therapy of the literature review until now. Meanwhile, there has been no increase in the incidence of adverse reactions; however, the research just organized 8 patients in the group, so the grouping proportion is small. Therefore, Freedman [6] reported that the additional amount of the same period of IMRT and clinical I period research on synchronously oral capecitabine, pelvic is 45 Gy/25 fractions. Tumor area synchronized with the amount of climbing, from 55 Gy to be increased into 65 Gy gradually. The first 8 patients completed 55 Gy radiotherapy, but 3 patients appeared to show 6 kinds of III toxic reaction, leading to termination of the dose escalation study, so the synchronized increasing should be cautious.

The first tomotherapy was officially used in clinical trials in 2003, adopting spiral CT to draw the images and the treatment of the tumor, and collect IGRT (Radiation therapy under the guidance of imaging) and IMRT (Conformal intensity modulation radiotherapy) together, to highlight the features of both therapy methods. Tomotherapy, combined with 360 degrees of photon incidence angle and the treatment of the bed of the synchronous movement, can be designed to modulate radiation therapy technology from 51 angles of the spiral intensity. Dose curves can be well adapted to the target region. Target edge dose shall be steep descent gradient. The shape of the pelvic area is irregular. A rugged target with a larger volume irradiation shall better reduce the normal tissue dose needed to be protected, reduce nausea, vomiting, radiation enteritis, bone marrow suppression, and other complication incidence. Under the premise of reaching the same target area coverage, tomotherapy was more uniform than conventional IMRT in the PTV target region. By each treatment before the image guide way, tomotherapy fixed the shift error of tumors or normal tissue, which makes tomotherapy treatment not only better in terms of target coverage, but it also can reduce the position error of the tumor.

Therefore, compared with conventional field irradiation, three-dimensional conformal radiotherapy, IMRT induced by non-image further reduced the volume of pGTV and GTV, reduces

the toxic side effects associated with irradiation [7-10, 22, 23]. The research adopted tomotherapy to implement SIB-IMRT with the purpose of using the dose feature of tomotherapy and protecting endangered organs.

In this group of patients the bladder filling state of the small intestine volume, combined with tomotherapy IMRT irradiation technology, and the endangered small intestine Dmax<54 Gy, V50≤5%, V30≤50%, V15≤150 ml; therefore, the side effects of gastrointestinal toxicity are small. The tumors of the patients are located in middle and lower rectum, CTV lower bound to the skin of the anal verge, which is the reason resulting in high skin III adverse reaction rate (62.5%). After the operation on 14 patients in this group, PCR reached 28.6% (4/14). The real PCR rate of 2 cases of clinical CR non-operational patients reached the maximum PCR rate of clinical experiment rate of rectal cancer neoadjuvant therapy [21].

Preliminary results of this study suggest that locally advanced removal middle and lower rectal cancer adopted spiral fault concurrent radiotherapy (SIB-IMRT) and synchronously oral capecitabine chemotherapy. The adverse reactions of blood system and gastrointestinal tract were mild, and the adverse reactions of skin and mucous membrane could be accepted. The rate of CCR and PCR was encouraging, which is expected to improve the local control rate. But because of the small number of patients, the observation period is short, and therefore the long-term effect is to be confirmed by large samples and long-term follow-up.

Disclosure of conflict of interest

None.

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