Original Article

Stage cT3 low rectal cancer: analysis of prognostic factors

Fan Li[1,2#], Jin-Hai Chen[3#], Yang Liu[4], Guo-Xian Guan[5], Chuan-Hui Lu[1,2]

[1]Department of Colorectal Surgery, The First Affiliated Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China; [2]The Third Clinical Medical College, Fujian Medical University, Fuzhou, China; [3]Department of Endoscopy Center, The First Affiliated Hospital of Xiamen University, Xiamen, China; [4]Department of Anesthesiology, The First Affiliated Hospital of Xiamen University, Xiamen, China; [5]Department of Colorectal Surgery, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China

Contributions: (I) Conception and design: F Li; (II) Administrative support: CH Lu; (III) Provision of study materials or patients: GX Guan; (IV) Collection and assembly of data: JH Chen; (V) Data analysis and interpretation: Y Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Chuan-Hui Lu. Department of Colorectal Surgery, The First Affiliated Hospital of Xiamen University, School of Medicine, Xiamen University, The Third Clinical Medical College, Fujian Medical University, Fujian, China. Email: 46601533@qq.com; Guo-Xian Guan. Department of Colorectal Surgery, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China. Email: gxguan1108@163.com.

Background: Whether all cT3 low rectal cancer patients should receive neoadjuvant chemoradiotherapy (nCRT) remains controversial. The depth of invasion beyond the muscularis propria of the cT3 rectal cancer is of great significance to the selection of a treatment plan and the evaluation of prognosis.

Methods: A retrospective analysis was conducted of 187 patients with stage cT3 low rectal cancer, who had been treated at the Department of Colorectal Surgery, The First Affiliated Hospital of Xiamen University from June 2010 to December 2012. The patients were divided into the nCRT group (88 cases) and no-nCRT group (99 cases). Possible significant prognostic factors [i.e., primary tumor volume (PTV), cell differentiation, circumferential resection margin (CRM), nCRT, age, sex, carcinoembryonic antigen (CEA), lymph node status, surgical procedure, etc.] were collected for estimation of disease-free survival (DFS), distant metastases rate (DM), local recurrence rate (LR). Independent predictive factors or survival were determined using Cox proportional hazards model.

Results: The mean PTV was 16.2±11.1 (2.07–72.68) cm^3. In the univariate and multivariate analyses: nCRT hazards ratio (HR) =4.258, 95% confidence interval (CI): 1.912–9.483 (P<0.001); PTV HR =0.381, 95% CI: 0.181–0.804 (P=0.011); CRM HR =0.227, 95% CI: 0.097–0.532 (P=0.001). For the PTV ≤15 cm^3 group, there were no significant differences between the nCRT and no-nCRT group in 3-year follow-up (P>0.05). For the PTV >15 cm^3 group, there were significant differences between the nCRT and no-nCRT group in 3-year DFS (84.2% *vs.* 51.1%; P=0.001), DM (13.1% *vs.* 31.2%; P=0.017) and LR (2.9% *vs.* 26.6%; P=0.009). For the CRM negative group, there were significant differences between the nCRT and no-nCRT group in 3-year DFS (94.0% *vs.* 79.0%; P=0.008), LR (1.5% *vs.* 10.7%; P=0.028) and DM (4.5% *vs.* 13.5%; P=0.039).

Conclusions: For stage cT3 low rectal cancer patients, nCRT, PTV, and CRM were independent prognostic factors. NCRT may improve the survival of PTV >15 cm^3 patients, but may not have a significant effect on patient with PTV ≤15 cm^3 and CRM negative. Direct surgery is recommended for this group of patients.

Keywords: Tumor volume; low rectal cancer; T3 stage; neoadjuvant chemoradiotherapy (nCRT); prognosis

Submitted Feb 09, 2022. Accepted for publication Apr 20, 2022.
doi: 10.21037/jgo-22-269
View this article at: https://dx.doi.org/10.21037/jgo-22-269

Introduction

Total mesorectal excision (TME) after neoadjuvant chemoradiotherapy (nCRT) has become the norm in the diagnosis and treatment of locally advanced rectal cancer. The National Comprehensive Cancer Network (NCCN) guidelines recommend nCRT for patients with stage cT3 low rectal cancer, but due to the many side effects of nCRT, the question of whether all cT3 patients should receive nCRT remains controversial. The depth of invasion beyond the muscularis propria of the rectum in cT3 rectal cancer patients is of great significance to the selection of a treatment plan and the evaluation of prognosis (1-3). Wong *et al.* reported that it might not be suitable for all cT3 rectal cancer patients to be evaluated based on the measurement of single diameter line (4). Our research has revealed primary tumor volume (PTV) significantly correlated with the depth of tumor infiltration mesorectum. We found that bigger tumor volume may lead to a worse prognosis (5). However, there are few studies on the relationship between PTV and nCRT in stage cT3 low rectal cancer.

According to the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for rectal cancer, circumferential resection margin (CRM) positive refers to the presence of cancer in the mesorectum fascia within 1 mm leading to an increased risk of local recurrence, distant metastases, and poorer survival (6).

The purpose of our study was to investigate the effects of prognosis factors nCRT, PTV and CRM, etc. to guide the individualized treatment of patients with stage cT3 low rectal cancer. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-269/rc).

Methods

Patients

In total, 187 patients with low rectal cancer were selected from the Department of Colorectal Surgery, The First Affiliated Hospital of Xiamen University from June 2010 to December 2012. The patients comprised 130 (69.5%) males and 57 (30.5%) females, with an average age of 57.2± 12.3 years. NCRT was used in 88 patients, and no-nCRT in 99 patients. The no-nCRT group was not routinely treated with nCRT because they refused or could not tolerate nCRT.

To be eligible for inclusion in the study, patients had to meet the following inclusion criteria: (I) have a tumor located below the peritoneal reflection line based on imaging and intraoperative judgment; (II) have a diagnosis of rectal adenocarcinoma as confirmed by a histological biopsy and pathology; (III) have undergone high-resolution magnetic resonance imaging (MRI) before treatment, and have stage cT3; (IV) have not undergone rectal surgery, chemotherapy, or pelvic radiation therapy, and have had no other malignancies, inflammatory bowel disease, or refractory severe disease in the last 5 years; (V) have no distant metastasis before treatment; and (VI) have undergone TME. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had cTNM stage IV; (II) had undergone an emergency operation, or a radical operation could not be performed; (III) had no high-resolution MRI data. All patients and their family members were informed and agreed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of The First Affiliated Hospital of Xiamen University [No. 2022 Scientific Research Ethics Examination Number (027)]. Individual consent for this retrospective analysis was waived.

MRI protocol and tumor volume measurement

The PTV was measured by high-resolution MRI and diffusion-weighted imaging (DWI). Imaging was obtained using Siemens Magnetom Trio Tim 3.0T MR scanner and phased array body coil. The MRI protocols included turbo spin-echo T2-weighted imaging (T2WI) in 3D directions (3-mm thickness, 0.6-mm spacing), and DWI in the axial direction (5-mm thickness, 1-mm spacing). The value of b in DWI was 800 s/mm^2. By tracing the apparent diffusion coefficient (ADC) in the oblique axial view, the tissue boundary was obtained in the region of the rectal cancer; that is, the region of interest (ROI). By analyzing each section to draw the ROI boundaries, and in calculating each ROI section area, the planar area of each slice was summed and multiplied by the 5-mm thickness and 1-mm layer spacing to obtain the final PTV of the rectal cancer (7) (see *Figures 1-3*). Each patient had a moderately full bladder, and was placed in the supine position before the scan. The images were processed by 2 experienced radiologists using the blind method, and the average of the 2 data was taken.

Patient characteristics

Positive lymph nodes with a diameter >3 mm, a margin

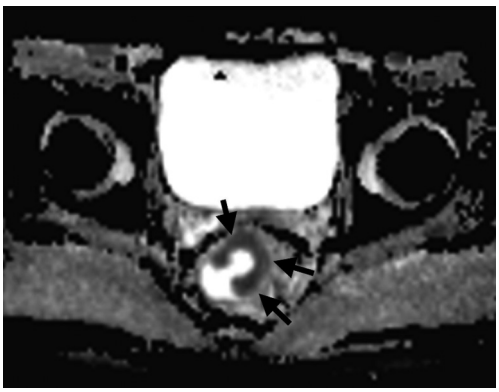

Figure 1 Apparent diffusion coefficient (ADC): tumor is located in rectum anterior wall, left lateral wall and back wall (black arrows).

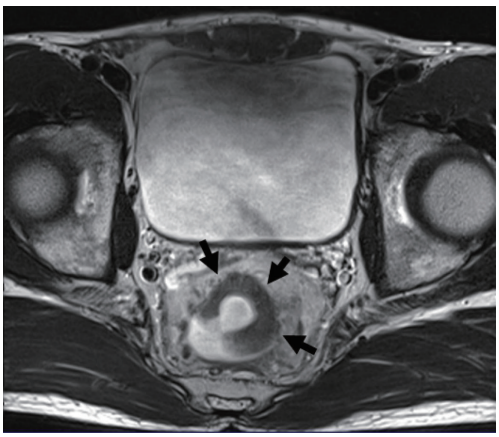

Figure 2 T2-weighted imaging (T2WI): tumor is located in rectum anterior wall, left lateral wall and back wall (black arrows).

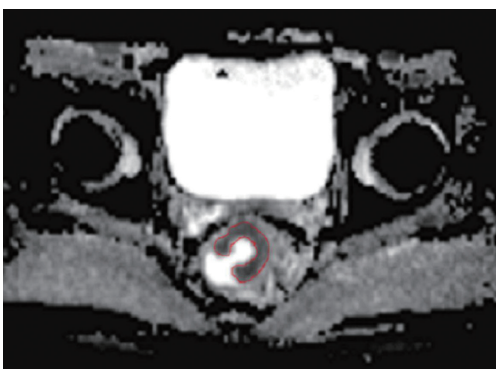

Figure 3 Apparent diffusion coefficient (ADC): the lesion boundary traced in red line represent the area of tumor from a certain level.

that is not smooth, or a heterogeneous signal intensity can be considered suspicious for metastasis. The evaluation of vascular wall invasion (EMVI) is defined as the presence of cancerous cells in the blood vessels outside the muscularis propria. The normal vascular wall around the rectum appears to be linear and zigzag in MRI-T2WI images. However, EMVI shows a tumor signal in the blood vessels, widened vessels, or a tumor that has expanded beyond and destroyed the wall (8).

The depth of rectal cancer infiltration beyond the muscularis propria was measured as both the distance between the muscularis propria, and the outermost border of the tumor. When the muscularis propria could not be identified, we measured the distance between the middle of 2 muscularis propria breaking points, and the outermost boundary of the tumor (9,10).

According to the pathological stage [International Union Against Cancer (UICC) TNM stage] (11), the tumor invades the muscularis propria in stage pT2, the tumor invasion is <5 mm beyond the muscularis propria in stage pT3a, the tumor invasion is 5–10 mm in stage pT3b, the tumor invasion is >10 mm in stage pT3c, and the tumor penetrates the peritoneal visceral layer in stage pT4.

Therapy

All patients were treated with radical resection of rectal cancer according to the TME principle. Patients who had been diagnosed as having an advanced tumor received nCRT according to the 2010 Chinese diagnostic and therapeutic criteria for colorectal cancer. The irradiation area included the primary lesion of the rectal tumor and the drainage area of the pelvic lymph nodes. The clinical target dose was 45 Gy/25 times, and the gross target dose was supplemented to 50.4 Gy/28 times. The patients received 5 consecutive days of irradiation and 2 days of rest per week for a total of 35 days. The patients concurrently received 2–3 cycles of xelox chemotherapy (including 130 mg/m^2 of oxaliplatin infused into the vein over 2 h on the first day, and 850–1,000 mg/m^2 of capecitabine taken orally twice daily for 14 days).

Clinical follow-up

Follow-up was conducted on an outpatient basis by telephone or e-mail. A physical examination, laboratory

Table 1 Comparing MRI valuation with postoperative pathological stage (the RSNA cT3-stage standard)

cT3	pT stage					Veracity (%)	Sensitivity (%)	Specificity (%)
	pT2 (n=4)	pT3a (n=100)	pT3b (n=52)	pT3c (n=13)	pT4 (n=10)			
T3a	4	96	24	2	5	78.2	73.3	91.7
T3b	0	4	28	11	5	75.4	58.3	81.6

MRI, magnetic resonance imaging; RSNA, Radiological Society of North America.

test, MRI of the pelvis and liver, and computed tomography of the chest were performed every 3–6 months. Local recurrence (LR) was defined as the presence of radiographic or histopathologic evidence of cancer recurrence confined to the pelvic area. Distant metastases (DM) included metastases to the liver, lung, bone, brain, kidney or other organs. DFS was described as the time of operation to the date of recurrence.

Statistical analysis

The data were analyzed using SPSS 19.0 on Windows. The enumeration data were tested by the Chi-square test or the Fisher exact-probability test. The survival curves were expressed using the Kaplan-Meier method, and statistically compared using the log-rank test. The Cox proportional-hazards model was used for the univariate and multivariate analysis. A P value <0.05 was considered statistically significant.

Results

Survival situation

The follow-up time was 36.5 (5.0–52.2) months, and the deadline was 2014-12-31. In total, 48 patients (25.7%) were found to have recurrence or metastasis after operation, 16 (8.5%) had LR, 29 (15.5%) had distant metastasis, 3 (1.6%) had LR and metastasis, 19 (10.2%) died due to the recurrence of rectal cancer, and 6 (3.2%) died due to other causes (e.g., accidents or other diseases). The 3-year DFS and overall survival rates for all patients were 74.3% and 86.6%, respectively.

Accuracy of MRI evaluation

The sensitivity, specificity, and accuracy of CRM judged by MRI were 85.7%, 90.6%, and 89.9%, respectively. The sensitivity, specificity and accuracy of EMVI involvement were 76.2%, 93.6%, and 89.9%, respectively. The results of the comparison of the concordance between the high-resolution MRI staging and the postoperative pathological analysis are set out in *Table 1*.

Effects of different factors on prognosis

Table 2 summarizes the information of the patients. In total, 187 patients were enrolled in the study with an average PTV of 16.2±11.1 (2.07–72.68) cm^3. The longest distance outside the muscularis propria was 3.8±3.1 [1–14] mm; positive correlation with PTV (r=0.581, P<0.001). Based on a PTV best cutoff point of 15 cm^3 (5), the patients were divided into the PTV ≤15 cm^3 group and the PTV >15 cm^3 group, which had 3-year DFS rates of 86.6% and 64.6% (P≤0.001), distant metastasis (DM) rates of 8.9% and 23.0% (P=0.001), and LR rates of 4.7% and 16.7% (P=0.004), respectively.

The CRM negative and CRM positive patients were compared, and had 3-year DFS rates of 82.1% and 49.7% (P≤0.001), DM rates of 11.5% and 36.0% (P=0.004), and LR rates of 9.1% and 32.4% (P=0.002), respectively. The association analysis showed that PTV was associated with CRM (P<0.001, r=0.352).

There were significant differences between the nCRT and no-nCRT groups in terms of the 3-year DFS rates (86.9% *vs.* 71.8%; P=0.007), the DM rates (9.7% *vs.* 19.0%; P=0.034), and the LR rate (3.6% *vs.* 12.5%; P=0.028). For the PTV ≤15 cm^3 group, there were no statistically significant differences between the nCRT and no-nCRT groups in terms of the 3-year DFS rates (86.8% *vs.* 85.7%; P=0.962), the DM rate% (7.4% *vs.* 9.7%; P=0.861), and the LR rates (4.1% *vs.* 5.0%; P=0.908). For the PTV >15 cm^3 group, there were significant differences between the nCRT and no-nCRT groups in terms of the 3-year DFS rates (84.2% *vs.* 51.0%; P=0.001), the DM rates (13.1% *vs.* 31.2%; P=0.017), and the LR rates (2.9% *vs.* 26.6%; P=0.009). For the CRM negative patients, there were

Table 2 Clinical data of 187 patients with low rectal cancer

Parameter	No-nCRT, n (%)	nCRT, n (%)	P value
N=187	99	88	
Age (year)			0.23
≤60	56 (49.1)	58 (50.9)	
>60	43 (58.9)	30 (41.1)	
Sex			0.427
Male	66 (50.8)	64 (49.2)	
Female	33 (57.9)	24 (42.1)	
PTV (cm^3)			0.459
≤15	55 (50.5)	54 (49.5)	
>15	44 (56.4)	34 (43.6)	
Infiltrate anterior wall			0.559
No	47 (50.5)	46 (49.5)	
Yes	52 (55.3)	42 (44.7)	
Cell differentiation			0.012
Low differentiated adenocarcinoma/mucinous adenocarcinoma/signet ring cell carcinoma	12 (85.7)	2 (14.3)	
Middle\high differentiated adenocarcinoma	87 (50.3)	86 (49.7)	
CEA (ng/mL)			<0.001
≤5.0	52 (41.9)	72 (58.1)	
>5.0	47 (74.6)	16 (25.4)	
CA199 (U/mL)			0.202
≤37	87 (51.2)	83 (48.8)	
>37	12 (70.6)	5 (29.4)	
ALB (g/L)			0.173
≤35	15 (68.2)	7 (31.8)	
>35	84 (50.9)	81 (49.1)	
Hb (g/L)			0.624
≤10	3 (75.0)	1 (25.0)	
>10	96 (52.5)	87 (47.5)	≤0.001
cT3N			<0.001
cN0	44 (72.1)	17 (27.9)	
cN+	55 (43.7)	71 (56.3)	
CRM			0.095
Negative	85 (55.9)	67 (44.1)	
Positive	14 (40.0)	21 (60.0)	

Table 2 (*continued*)

Table 2 (*continued*)

Parameter	No-nCRT, n (%)	nCRT, n (%)	P value
Surgery			0.58
SPS	6 (42.9)	8 (57.1)	
APR	93 (53.8)	80 (46.2)	

nCRT, neoadjuvant chemoradiotherapy; PTV, primary tumor volume; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; ALB, albumin; Hb, hemoglobin; CRM, circumferential resection margin; SPS, sphincter-preserving surgery; APR, abdominoperineal resection.

Table 3 nCRT affects the prognosis of cT3 patients with low rectal cancer (Kaplan-Meier method)

Group	Disease-free survival rate		Distant metastases rate		Local recurrence rate	
	3-year (%)	P value	3-year (%)	P value	3-year (%)	P value
Total cT3		0.007		0.034		0.028
nCRT	86.9		9.7		3.6	
No nCRT	71.8		19		12.5	
PTV ≤15 cm^3		0.962		0.861		0.908
nCRT	86.8		7.4		4.1	
No nCRT	85.7		9.7		5	
PTV >15 cm^3		0.001		0.017		0.009
nCRT	84.2		13.1		2.9	
No nCRT	51		31.2		26.6	
CRM-negative		0.141		0.211		0.293
nCRT	81.2		8.9		4.5	
No nCRT	79		13.5		12.8	
CRM-positive		0.003		0.015		0.011
nCRT	62.6		28		25	
No nCRT	28.6		56		43.6	
PTV >15 cm^3 and CRM negative		0.019		0.045		0.075
nCRT	89.6		5.9		4.8	
No nCRT	61		22.5		21.5	

nCRT, neoadjuvant chemoradiotherapy; PTV, primary tumor volume; CRM, circumferential resection margin.

significant differences between the nCRT and no-nCRT groups in terms of the 3-year DFS rates (81.2% *vs.* 79.0%; P=0.141), the DM rates (8.9% *vs.* 13.5%; P=0.211), and the LR rates (4.5% *vs.* 12.8%; P=0.293). For the CRM positive patients, there were significant differences between the nCRT and no-nCRT groups in terms of the 3-year DFS rates (62.6% *vs.* 28.6%; P=0.003), the DM rates (28.0% *vs.* 56.0%; P=0.015), and the LR rates (25% *vs.* 43.6%; P=0.011) (see *Table 3*).

Univariate and multivariate analysis

The Cox regression model was used to analyze the risk factors for 3-year DFS in patients with stage cT3 low rectal

cancer. The results showed that nCRT, CRM, and PTV were influencing factors and independent predictors of DFS [nCRT hazards ratio (HR) =4.258, 95% confidence interval (CI): 1.912–9.483, P<0.001; PTV HR =0.381, 95% CI: 0.181–0.804, P=0.011; CRM HR =0.227, 95% CI: 0.097–0.532, P=0.001; see *Table 4*].

Discussion

Radical resection is the treatment of choice for rectal cancer. TME surgery after nCRT has become the standard treatment for locally advanced rectal cancer patients (stage T3, T4, or N1, N2). The NCCN guidelines recommended nCRT for patients with stage cT3 low rectal cancer (12), but Taylor *et al.* are of the view that it is unnecessary for very early patients (i.e., those with infiltration above the muscularis propria <5 mm, those who are CRM negative, or those who have no lymph node metastasis) who could benefit from surgical excision alone (with a LR rate of 3% and a 5-year DFS of 85%) (13). Thus, treating all cT3 patients with nCRT remains controversial.

The depth at which rectal cancer infiltrates outside the muscular propria has substantial clinical significance, which could guide the prognosis and options for preoperative treatment. At present, the UICC has proposed standard concrete subgroups of cT3 low rectal cancer (T3a: <1 mm; T3b: 1–5 mm; T3c: >5–15 mm; and T3d, >15 mm) (14). However, radiologists have found that it is a great challenge to measure the depth of tumor invasion outside the muscular propria <1 mm, as the surrounding cells react to fibrosis, and inflammation may affect the accuracy of the assessment. Even If high-resolution MRI is used for the evaluations, there are differences among radiologists (15). The Radiological Society of North America (RSNA) has the following classification for cT3 stages: T3a: <5 mm; T3b: 5–10 mm; and T3c: >10 mm (16). Conversely, the standard of the UICC staging system is too detailed, and the mesentery of Chinese patients is thinner.

Under the RSNA standard, the number of cases in group T3c was less (8/187, 4.3%). Wong *et al.* measured the thickness of the mesorectum in 25 Chinese patients, and found that the distances from the anus were 5, 7.5, and 10 cm, and the corresponding average thickness measurements of the anterior wall of the rectum were 1, 3, and 3.7 mm, respectively (4). Kim *et al.* studied 66 patients with rectal cancer below the peritoneum, and found the average thickness of the anterior mesorectum was 2.6 (0–11.4) mm, and speculated that that the thickness of the anterior mesorectum affects the accuracy of MRI in judging the depth of tumor infiltration in the anterior wall of the rectum (17). These studies suggest that MRI sub-staging based on a single-slice measurement may not be applicable to all low rectal cancer patients, especially if the tumor is located in the anterior wall. Overall information about the tumor, including its transverse and longitudinal growth (i.e., the 3D volume) may provide a more comprehensive understanding of the anatomic expansion of the tumor.

PTV was significantly correlated with the longest distance of tumor invasion beyond the muscularis propria of the rectum (P<0.001, r=0.581). Thus, PTV may be able to be used as a new parameter to guide the individualized treatment of cT3 low rectal cancer patients. A tumor, node, metastasis (TNM) analysis provides qualitative data of changes in the assessment of the tumor situation, while tumor volume can be considered a quantitative change (18).

High-resolution MRI provides details of the 3D spatial structure, and can be used in clinical settings as a reliable technical means to measure the volume of a tumor. The value of the volume measurement tends to indicate the actual size and stability. Notably, T2WI can be used not only to measure the ADC, but also to provide information about tumor density, internal structure, and envelope integrity (19). The ROI volume measurement is based on high-resolution MRI. It takes time to process imaging data; however, MRI can detect subtle morphological changes in tumors, and accurately describe tumor outlines. Thus, at present, MRI is a more accurate method for obtaining tumor volume measurements (20). Notably, MRI is not accurate at determining tumor boundaries in patients after nCRT. Thus, in this study, we conducted a pre-treatment high-resolution MRI analysis.

In our study, the patients were divided into the PTV ≤15 cm^3 and PTV >15 cm^3 groups, and had 3-year DFS rates of 88.3% and 57.3%, respectively; the difference was statistically significant (P<0.001). Merkel *et al.* found that the prognosis of rectal cancer with <1 mm of invasion beyond the muscularis propria (T3a) is consistent with that of T2, the 5-year DFS of rectal cancer patients with <5 mm of invasion beyond the muscularis propria is >85%, and when the invasion is obviously >5 mm, the 5-year DSF is approximately 54% (2). Shin *et al.* reported that the progression-free survival rates of T3a (<1 mm), T3b (1–5 mm), T3c (5–15 mm), T3d (≥15 mm) were 86.5%, 74.2%, 58.3%, and 29%, respectively (P<0.001). Thus,

Table 4 Univariate and multivariate analysis of the prognostic significance of clinical factors on 3-year DFS outcomes

Parameter	Univariate analyses		Multivariate analyses	
	HR value (95% CI)	P value	HR value (95% CI)	P value
Age (year)	0.840 (0.456–1.550)	0.577		
≤60				
>60				
Sex	1.162 (0.595–2.270)	0.66		
Male				
Female				
nCRT	2.498 (1.254–4.977)	0.009	4.258 (1.912–9.483)	0
Yes				
No				
PTV (cm^3)	0.281 (0.146–0.540)	0	0.381 (0.181–0.804)	0.011
≤15				
>15				
Infiltrate anterior wall	0.756 (0.410–1.393)	0.369		
Yes				
No				
CEA (ng/mL)	0.584 (0.318–1.073)	0.083		
≤5.0				
>5.0				
CA199 (U/mL)	0.550 (0.232–1.306)	0.175		
≤37				
>37				
ALB (g/L)	1.363 (0.573–3.241)	0.483		
≤35				
>35				
Hb (g/L)	1.023 (0.141–7.442)	0.982		
≤10				
>10				
Cell differentiation	1.756 (0.690–4.471)	0.237		
Low differentiated adenocarcinoma/mucinous adenocarcinoma/signet ring cell carcinoma				
Middle/high differentiated adenocarcinoma				
cN stage	1.039 (0.689–1.567)	0.856		
cT3N0				
cT3N+				

Table 4 (*continued*)

Table 4 (*continued*)

Parameter	Univariate analyses		Multivariate analyses	
	HR value (95% CI)	P value	HR value (95% CI)	P value
CRM	0.244 (0.131–0.455)	0	0.227 (0.097–0.532)	0.001
Negative				
Positive				
Surgery	0.970 (0.300–3.142)	0.96		
SPS				
APR				

DFS, disease-free survival; CI, confidence interval; nCRT, neoadjuvant chemoradiotherapy; PTV, primary tumor volume; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; ALB, albumin; Hb, hemoglobin; CRM, circumferential resection margin; SPS, sphincter-preserving surgery; APR, abdominoperineal resection.

when rectal cancer extends beyond muscularis propria ≤5 or >5 mm, the survival rate is significantly different between the 2 groups (1). In this study, the Chinese mesorectum was thinner, the number of T3c cases was small, the cT3 patients were divided into T3a and T3b+c, and the conclusions we reached in our study are consistent with the views of the scholars mentioned above.

NCRT can produce adverse reactions, such as bone marrow suppression and nervous system and gastrointestinal complications, and excessive treatment inevitably places a burden on patients. If the accurate staging management of cT3 rectal cancer is conducted before treatment, the treatment mode of patients can be optimized. When the PTV was ≤15 cm^3, the difference in 3-year DFS rates between the nCRT and no-nCRT groups was not statistically significant; thus, nCRT did not improve outcomes in this group (P=0.962). When the PTV was >15 cm^3, the prognosis of the nCRT group was better than that of the no-nCRT group (P=0.001). Of the patients with a PTV ≤15 cm^3 who were CRM positive, only 6 cases were selected. The association analysis showed that PTV is associated with CRM (P<0.001), which suggests that when the PTV is ≤15 cm^3, the CRM positive rate may be low. Of the patients with a PTV >15 cm^3 who were CRM negative, the curative effect of the nCRT group was better than that of the no-nCRT group. Due to the large error in judging metastatic lymph nodes by MRI, the study will not discuss.

Conclusions

The study was a retrospective analysis and had some limitations. The end point was 3-year survival. The reproducibility of the PTV measurements is a problem that restricts the further promotion and application of this study. With the cooperation of the software development center, target area reconstruction and the PTV can be obtained automatically by computer, which will greatly improve the clinical application of the PTV. The PTV may be used as a cT3 low rectal cancer additional parameter for subgrouping. NCRT may improve the prognosis of patients with a PTV >15 cm^3, but may not have a significant effect on patients with a PTV ≤15 cm^3 and CRM negative. Direct surgery is recommended for this group of patients.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-269/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-269/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-269/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of The First Affiliated Hospital of Xiamen University [2022 Scientific Research Ethics Examination Number (027)]. Individual consent for this retrospective analysis was waived.

References

1. Shin R, Jeong SY, Yoo HY, et al. Depth of mesorectal extension has prognostic significance in patients with T3 rectal cancer. Dis Colon Rectum 2012;55:1220-8.
2. Merkel S, Mansmann U, Siassi M, et al. The prognostic inhomogeneity in pT3 rectal carcinomas. Int J Colorectal Dis 2001;16:298-304.
3. Zhang X, Lu Q, Guo X, et al. Better prognostic determination of cT3 rectal cancer through measurement of distance to mesorectal fascia: A multicenter study. Chin J Cancer Res 2021;33:606-15.
4. Wong EM, Lai BM, Fung VK, et al. Limitation of radiological T3 subclassification of rectal cancer due to paucity of mesorectal fat in Chinese patients. Hong Kong Med J 2014;20:366-70.
5. Li F, Guan G, Lin W, et al. The prognostic significance of primary tumor volume by MRI in cT3 low rectal cancer. Chinese Journal of Practical Surgery 2019;39:365-9.
6. Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol 2012;23:2479-516.
7. Genovesi D, Filippone A, Ausili Cèfaro G, et al. Diffusion-weighted magnetic resonance for prediction of response after neoadjuvant chemoradiation therapy for locally advanced rectal cancer: preliminary results of a monoinstitutional prospective study. Eur J Surg Oncol 2013;39:1071-8.
8. Chandramohan A, Mittal R, Dsouza R, et al. Prognostic significance of MR identified EMVI, tumour deposits, mesorectal nodes and pelvic side wall disease in locally advanced rectal cancer. Colorectal Dis 2021 [Epub ahead of print]. doi:10.1111/codi.16032.
9. Shirouzu K, Akagi Y, Fujita S, et al. Clinical significance of the mesorectal extension of rectal cancer: a Japanese multi-institutional study. Ann Surg 2011;253:704-10.
10. Miyoshi M, Ueno H, Hashiguchi Y, et al. Extent of mesorectal tumor invasion as a prognostic factor after curative surgery for T3 rectal cancer patients. Ann Surg 2006;243:492-8.
11. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017;67:93-9.
12. Benson AB, Venook AP, Al-Hawary MM, et al. NCCN Guidelines Insights: Rectal Cancer, Version 6.2020. J Natl Compr Canc Netw 2020;18:806-15.
13. Taylor FG, Quirke P, Heald RJ, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. Ann Surg 2011;253:711-9.
14. Yoo HY, Shin R, Ha HK, et al. Does t3 subdivision correlate with nodal or distant metastasis in colorectal cancer? J Korean Soc Coloproctol 2012;28:160-4.
15. Kaur H, Choi H, You YN, et al. MR imaging for preoperative evaluation of primary rectal cancer: practical considerations. Radiographics 2012;32:389-409.
16. Engelen SM, Beets-Tan RG, Lahaye MJ, et al. MRI after chemoradiotherapy of rectal cancer: a useful tool to select patients for local excision. Dis Colon Rectum 2010;53:979-86.
17. Kim YW, Cha SW, Pyo J, et al. Factors related to preoperative assessment of the circumferential resection margin and the extent of mesorectal invasion by magnetic resonance imaging in rectal cancer: a prospective comparison study. World J Surg 2009;33:1952-60.
18. Pierredon-Foulongne MA, Nougaret S, Bibeau F, et al. Utility of reassessment after neoadjuvant therapy and difficulties in interpretation. Diagn Interv Imaging 2014;95:495-503.
19. Roth Y, Tichler T, Kostenich G, et al. High-b-value diffusion-weighted MR imaging for pretreatment prediction and early monitoring of tumor response to

therapy in mice. Radiology 2004;232:685-92.
20. Mayr NA, Taoka T, Yuh WT, et al. Method and timing of tumor volume measurement for outcome prediction in cervical cancer using magnetic resonance imaging. Int J Radiat Oncol Biol Phys 2002;52:14-22.

(English Language Editor: L. Huleatt)

Cite this article as: Li F, Chen JH, Liu Y, Guan GX, Lu CH. Stage cT3 low rectal cancer: analysis of prognostic factors. J Gastrointest Oncol 2022;13(2):672-682. doi: 10.21037/jgo-22-269

