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Prognostic factors in patients with complete response of the tumour (ypT0) after neoadjuvant chemoradiotherapy and radical resection of rectal cancer

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Key words

lymph node, neoadjuvant chemoradiotherapy, prognostic factor, rectal cancer, ypT0.

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Introduction

The treatment of locally advanced mid-lower rectal cancer consists of neoadjuvant chemoradiotherapy (NCRT), operation and adjuvant chemoradiotherapy.^{1,2} According to the literature, 11.4–27% of patients after NCRT have pathological complete response (PCR).^{3,4} Compared with non-PCR patients, local recurrence and distant metastasis rates in PCR patients have been reported to be lower and in addition, disease-free survival (DFS) was prolonged.^{5,6} It still remains controversial whether rectal cancer patients with clinical complete response after NCRT should receive radical resection. Transanal local excision and a ‘watch-and-wait’ strategy can preserve the anal canal and avoid a permanent stoma. However, in the event of a local recurrence in the latter option, even if radical resection is performed in a

Abstract

Background: There are only a few studies on the prognosis of patients with complete response of the tumour (ypT0) after neoadjuvant chemoradiotherapy (NCRT) and radical resection of rectal cancer. The aim of the study was to identify prognostic factors with regard to oncological outcome in ypT0 patients after NCRT and radical resection.

Methods: All ypT0 patients with rectal cancer after NCRT and radical resection between January 2010 and June 2019 were included. Cox univariate and multivariate regression analyses were used to determine the prognostic factors of these patients.

Results: Seventy-six patients with ypT0 rectal cancer were included. In nine patients (11.8%), lymph node metastasis was identified. Age, gender, elevated carcinoembryonic antigen (CEA) and ypN+ were risk factors associated with a worse 5-year disease-free survival (DFS) rate in univariate analysis ($P = 0.08, 0.14, 0.007$ and 0.003 , respectively). In multivariate analysis, ypN+ and elevated CEA before NCRT were independent risk factors for worse 5-year DFS ($P = 0.005$ and 0.021 , respectively). Elevated CEA before NCRT, post-operative chemotherapy and ypN+ were risk factors associated with worse overall survival in univariate analysis ($P = 0.14, 0.002$ and 0.17 , respectively). However, in multivariate analysis, none of these three factors were independent risk factors for worse overall survival ($P = 0.20, 0.34$ and 0.06 , respectively).

Conclusion: ypN+ and elevated CEA before NCRT were found to be independent risk factors for an unfavourable DFS in ypT0 patients with complete response of the tumour after neoadjuvant chemoradiotherapy for rectal cancer.

timely manner, the incidence of developing distant metastasis will be increased.⁷ Therefore, identifying risk factors for local or distant recurrence in patients with complete response of the rectal tumour after NCRT would be highly valuable in the decision to proceed to either resection or watch-and-wait approach.

The aim of the current study was to identify the risk factors for worse prognosis in ypT0 patients after NCRT for rectal cancer.

Methods

Patient selection

A total of 448 patients with proven middle or low rectal cancer received NCRT and radical resection in our hospital between January 2010 and June 2019. Patients with distant metastasis and

patients who received systematic chemotherapy or radiotherapy in the past as well as patients who received chemotherapy alone for rectal cancer were excluded. There were 76 patients (17.0%) with post-operative pathological complete response of the tumour (ypT0) and these patients were included for analysis in the current study. A total of 64 patients had a cT3/4 or N+ on pre-treatment magnetic resonance imaging and in addition, 12 patients had T2N0 low rectal cancer on magnetic resonance imaging and received chemoradiation therapy with the aim to avoid abdominoperineal resection and preservation of the sphincter. This retrospective study was conducted at the Department of Colorectal Surgery, Changhai Hospital, Shanghai, China. It was performed in accordance with the ethical standards of Changhai Hospital Research Committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in this study.

Therapeutic regimen

All patients received intensity-modulated radiation therapy before surgery: a total dose of 45–50.4 Gy (1.8–2.0 Gy per fraction, 25–28 fractions) combined with chemotherapy consisting of capecitabine (825 mg/m² orally, twice daily, throughout the course of radiotherapy). When the tumour had good but not yet complete response after NCRT, patients received either Capox or FOLFOX while waiting for operation so as to improve the PCR rate (after radiotherapy: capecitabine 1000 mg/m² orally, twice daily; leucovorin 400 mg/m² intravenous infusion for 2 h, day 1; 5-Fu 400 mg/m² intravenous bolus, day 1, then 1200 mg/m²/day × 2 days continuous intravenous infusion; oxaliplatin 85 mg/m² intravenously, day 1). Surgery was planned 5–13 weeks after the completion of radiotherapy. Surgical procedures included low anterior resection and abdominoperineal resection. Patients with clinical stage II and III before NCRT received post-operative chemotherapy, Capox or FOLFOX, also depending on the preoperative regimen, unless patients were not fit enough for adjuvant chemotherapy, refused or were not able to pay the costs.

Follow-up

Follow-up data were retrospectively obtained from the medical records. The follow-up ended on 21 July 2019. All patients were followed up every 3 months for the first 2 years, every 6 months for the next 3 years and once a year thereafter. Digital rectal examination, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9, computed tomography of chest/abdominal/pelvis and abdominal ultrasound were performed every 3–6 months for the first 2 years. Complete colonoscopy was performed every year.

Statistical analysis

All statistical analyses were performed using SPSS Statistics 22.0 (IBM, Armonk, NY, USA). Categorical values were reported as frequency and percentage, and continuous values were reported as mean and standard deviation or median with range, depending on whether the values were normally distributed. To identify independent predictors of overall survival (OS) and DFS, univariate and

multivariate analyses were performed by using the Cox proportional hazard model. The hazard ratio, 95% confidence interval (CI) and *P*-value were reported for every variable identified as independent predictor of survival. *P* < 0.05 (two sides) was considered statistically significant.

Results

Clinicopathological characteristics

The baseline characteristics of all included 76 patients are described in Table 1. All patients underwent long-course radiotherapy for 5 weeks and all patients had simultaneously oral capecitabine. A total of 33 patients received Capox and seven received FOLFOX after radiation. The preoperative Capox or FOLFOX was given for two cycles on average, in addition to simultaneous oral capecitabine along with the radiotherapy. All patients had R0 resection. Post-operative pathological examination showed that 67 patients (88.2%) had ypT0N0. In nine patients (11.8%), the primary tumour had complete response, but either the mesorectal lymph nodes were positive or there were tumour deposits in the mesorectum. As tumour deposits are treated similarly as positive lymph nodes,⁸ those patients were added to the ypN+ group (*n* = 9). The average number of retrieved lymph nodes was 9.1 (range 1–21) for the 76 patients with ypT0 rectal cancer. Forty-eight patients had less than 12 lymph nodes in the specimen despite repeat review of the specimen if <12 lymph nodes were found during the first pathological evaluation. A total of 48 patients (63.2%) received adjuvant chemotherapy; only 18 patients (23.7%) received oral capecitabine and 30 patients (39.5%) received Capox or FOLFOX. Of the nine patients with positive lymph nodes, five received post-operative chemotherapy and four did not.

Univariate analysis

The median follow-up was 38.4 (range 2.0–103.1) months. Eighteen patients had a follow-up of less than 2 years, which is 23.7% of the included patients. Univariate analysis showed that ypN+ (*P* = 0.003) and elevated serum CEA before treatment (*P* = 0.007) were risk factors for worse 5-year DFS, and ypN+ (*P* = 0.002) was a risk factor for worse 5-year OS (Table 2). For high or moderately differentiated patients (*n* = 30), the 5-year DFS and OS were 90.0% and 95.0%, respectively. For low differentiated patients (*n* = 16), the 5-year DFS and OS were 87.1% and 100%, respectively. No significant difference was found between high/moderate versus less differentiated patients in univariate analysis (*P* = 0.53 for DFS, *P* = 0.48 for OS).

The 5-year DFS of patients with preoperative chemotherapy was not significantly different from the patients without preoperative chemotherapy (81.8% and 91.4%, respectively, *P* = 0.76). The 5-year OS rate was 92.6% and 96.7% in these two groups, respectively (*P* = 0.52). The 5-year DFS rate in post-operative chemotherapy and non-chemotherapy group was 86.4% and 85.5%, respectively (*P* = 0.47).

No significance difference was found between the group with <12 or at least 12 lymph nodes in OS (95.3% and 94.1%,

Table 1 Baseline characteristics

Characteristics	n = 76
Age (years, mean ± SD)	56.0 ± 10.3
Sex (%)	
Male	60 (78.9)
Female	16 (21.1)
Tumour position (cm, mean ± SD) [†]	4.1 ± 2.4
BMI	
<25	52 (68.4)
≥25	24 (31.6)
Clinical tumour stage [‡] (%)	
cT2	19 (25.0)
cT3	37 (48.7)
cT4	20 (26.3)
Clinical lymph node stage [§] (%)	
cN0	27 (35.5)
cN1	28 (36.8)
cN2	21 (27.6)
CEA at diagnosis (ng/mL, mean ± SD)	9.7 ± 18.7
Tumour differentiation ^{††} (%)	
Good	1 (1.3)
Moderate	29 (38.2)
Poor	16 (21.1)
Missing	30 (39.5)
Preoperative treatment (%)	
NCRT	36 (47.4)
NCRT + Capox or FOLFOX	40 (52.6)
Time to surgery after neoadjuvant radiotherapy (%)	
<6 weeks	9 (11.8)
6–8 weeks	18 (23.7)
>8 weeks	49 (64.5)
Surgical procedure (%)	
Abdominoperineal resection	21 (27.6)
Low anterior resection with diverting ostomy	49 (64.5)
Low anterior resection without ileostomy	6 (7.9)
Number of lymph nodes retrieved during surgery (mean ± SD)	9.1 ± 5.0
ypN (%)	
ypN–	67 (88.2)
ypN+	9 (11.8)
Post-operative adjuvant chemotherapy (%)	
None	28 (36.8)
Oral capecitabine	18 (23.7)
Capox or FOLFOX	30 (39.5)

[†]Distance between the inferior tumour margin and the anal verge.

[‡]T stage before NCRT.

[§]Lymph node stage before NCRT.

^{||}CEA level before treatment.

^{††}Tumour differentiation at biopsy before NCRT.

BMI, body mass index; CEA, carcinoembryonic antigen; NCRT, neoadjuvant chemoradiotherapy.

respectively, $P = 0.83$) or in DFS (91.0% and 77.6%, respectively, $P = 0.63$).

Of the nine patients with positive pathological lymph nodes, the 5-year DFS for patients with and without adjuvant chemotherapy was 80.0% and 33.3%, respectively ($P = 0.22$), and 5-year OS was 100% and 33.3%, respectively ($P = 0.056$). In the nine patients with positive lymph nodes, seven had body mass index (BMI) ≥25 and two had BMI <25. For these two groups of patients, the 5-year DFS was 50% and 100%, respectively ($P = 0.27$), and the 5-year OS was 66.7% and 100%, respectively ($P = 0.47$).

Of the 22 cases with CEA >5 ng/mL before NCRT, six had BMI ≥25 and 16 had BMI <25. The 5-year DFS rates in these two

groups were 53.3% and 81.3%, respectively ($P = 0.54$) and the 5-year OS rates were 80.0% and 93.8%, respectively ($P = 0.64$).

Multivariate analysis

In multivariate analysis, elevated serum CEA before treatment and ypN+ were independent risk factors for worse DFS, but no risk factors were found for OS (Tables 3,4).

Discussion

In ypT0 rectal cancer patients with complete response of the tumour after NCRT, 11.8% still had lymph node metastasis or tumour deposits in the mesorectum. ypN+ and elevated CEA before NCRT were independent risk factors of worse DFS.

In the current study, of the 67 ypT0N0 patients, no local recurrence occurred and the 5-year DFS and OS rates were 89.3% and 97.6%, respectively. This is comparable to the study by de Campos-Lobato *et al.*,⁵ which showed that in 58 patients who achieved PCR after NCRT, no local recurrence occurred during a median follow-up of more than 4 years and the 5-year OS rate was 93%. A multicentre study of 566 patients with ypT0N0 after NCRT in 36 centres found that after a median follow-up of 46.4 months, the local recurrence rate, distant metastasis rate, 5-year DFS and OS rates were 1.6%, 8.9%, 85% and 90%, respectively.⁹ However, in the nine patients with ypN+ (11.8%) in the current study, DFS and OS rates were worse (62.5% and 72.9%, respectively), and ypN+ was identified as an independent risk factor for ypT0 patients in terms of DFS but not for OS. Lu *et al.* analysed 59 patients with ypT0 after NCRT for rectal cancer, and found that there were eight cases (13.6%) of mesorectal lymph node metastasis, and patients with ypT0N0 had better 5-year recurrence-free survival and OS than ypT0N+ patients.¹⁰ Multivariate analysis also showed that mesorectal ypN+ was an independent influencing factor of recurrence-free survival in their study.¹⁰ Among the 91 patients with ypT0 analysed by Jang *et al.*, multivariate analysis also showed ypN+ as independent risk factor for 5-year DFS but not for OS.¹¹ This is consistent with the results of the current study that pN+ was identified as an independent risk factor of worse prognosis in terms of DFS but not OS for ypT0 patients. According to the literature, the distant metastasis rate of PCR patients after NCRT is reduced.¹² However, metastatic lymph nodes might not completely disappear as the primary lesion does. This might be due to the continuous evolution of tumour cells in the primary tumour and metastatic site, with the improving ability of invasion, haematogenous metastasis and chemoradiotherapy resistance.^{13,14} Therefore, even if the primary lesion of the intestinal wall disappears completely, the tumour cells from the metastasized lymph nodes might survive and cause distant metastasis.

This study also found that elevated CEA before treatment was an independent risk factor for DFS in patients with ypT0. CEA is encoded by CEACAM 5 gene and is a complex glycoprotein of the immunoglobulin gene super family. It is present on the surface of gastrointestinal cells, and only a small amount of serum CEA can be detected in the normal population.^{15,16} Although 80–90% of colorectal tumours produce CEA, only 40% of patients with

Table 2 Univariate analysis of 5-year DFS and OS in patients with ypT0

Variable	Total (n = 76)	Recurrence	DFS (%)	P-value	Death	OS (%)	P-value
Age				0.08			0.67
≤55	33	1	96.7		1	95.5	
>55	43	6	76.2		2	94.3	
Sex				0.14			0.64
Male	60	4	91.2		2	95.9	
Female	16	3	71.4		1	90.9	
BMI				0.46			0.99
<25	52	4	91.3		2	95.4	
≥25	24	3	72.0		1	94.1	
Tumour position [†]				0.88			0.70
≤5	56	5	88.3		2	95.0	
>5	20	2	81.4		1	93.8	
cT				0.56			0.77
cT2	19	1	93.8		1	93.3	
cT3–4	57	6	85.6		2	95.2	
cN				0.55			0.16
cN0	27	2	89.8		1	100	
cN1–2	49	5	82.9		2	91.2	
CEA [‡] (ng/mL)				0.007			0.14
≤5	54	2	92.8		1	97.5	
>5	22	5	71.0		2	86.6	
Preoperative treatment				0.76			0.52
NCRT	35	4	81.8		1	96.7	
NCRT + Capox or FOLFOX	41	3	91.4		2	92.6	
Time interval [§] (weeks)				0.82			0.89
≤8	26	3	83.2		1	95.4	
>8	50	4	89.0		2	94.3	
Surgical procedure				0.89			0.87
Low anterior resection	55	5	84.8		1	94.7	
Abdominoperineal resection	21	2	87.3		2	94.6	
Number of retrieved lymph nodes				0.63			0.83
<12	48	4	91.0		2	95.3	
≥12	28	3	77.6		1	94.1	
ypN				0.003			0.002
ypN–	67	4	89.3		1	97.6	
ypN+	9	3	62.5		2	72.9	
Post-operative treatment				0.49			0.17
Chemotherapy	48	4	86.4		1	97.1	
No chemotherapy	28	3	85.5		2	89.9	

[†]Distance between the anal verge and the inferior tumour margin.

[‡]CEA before neoadjuvant treatment.

[§]Time to surgery after neoadjuvant radiotherapy (weeks).

BMI, body mass index; CEA, carcinoembryonic antigen; DFS, disease-free survival; NCRT, neoadjuvant chemoradiotherapy; OS, overall survival.

colorectal cancer have elevated serum CEA.¹⁷ Previous studies have shown that increased preoperative CEA is a prognostic marker for both local and metastatic colorectal cancers.^{16,18} Lee *et al.* found that patients with CEA ≤5 ng/mL before treatment had significantly higher 5-year DFS than patients with CEA >5 ng/mL (73.2% versus 60.9%, $P = 0.002$).¹⁹ This was mainly due to a higher distant metastasis rate in the CEA >5 ng/mL group ($P = 0.013$) as there was no significant difference in local recurrence rate ($P = 0.732$).¹⁹ A meta-analysis by Colloca *et al.* investigated the relationship between pre-treatment CEA and oncological prognosis and showed that patients with normal CEA before treatment had significantly longer DFS (odds ratio 1.88, 95% CI 1.64–2.16) and also longer OS (odds ratio 1.85, 95% CI 1.38–2.48) compared with the group with elevated CEA.²⁰ However, in the current study, elevated CEA before treatment was only associated with longer DFS but not with OS. This may be due to relatively small sample size in the current study. Numerous studies have

concluded that elevated CEA has a worse prognosis and is an expression of subclinical metastases.^{19,21,22} Further studies confirmed that CEA affects the biological behaviour of tumour cells in an autocrine manner, increases tumour cell survival rate, inhibits tumour cell differentiation and promotes endothelial cell activation and tumour angiogenesis in a paracrine manner.^{23,24} The current study also confirms the prognostic value of CEA for worse DFS before NCRT and surgical treatment of rectal cancer.

The number of retrieved lymph nodes varies between individuals, depending on factors such as age, gender, tumour location and preoperative chemoradiotherapy.^{25–27} Radiotherapy leads to lymphocyte apoptosis, which is further replaced by fibrotic tissue, making lymph nodes more difficult to detect.^{28–31} Habr-Gam *et al.* found that the decreased number of retrieved lymph nodes was not associated with worse tumour prognosis; the 5-year DFS rate with the number of lymph nodes <12 was not statistically significantly different from the ypN0 group with an adequate number of lymph

Table 3 Multivariate analysis of DFS in patients with ypT0

Variable	Total	Hazard ratio	95% confidence interval	P-value
Age		6.87	0.64–74.16	0.11
≤55	33			
>55	43			
Sex		4.10	0.76–22.12	0.10
Male	60			
Female	16			
CEA [†] (ng/mL)		8.40	1.38–51.15	0.021
≤5	54			
>5	22			
ypN		14.45	2.29–91.21	0.005
ypN–	67			
ypN+	9			

[†]CEA before neoadjuvant treatment.

CEA, carcinoembryonic antigen; DFS, disease-free survival.

nodes retrieved (74% versus 59%, $P = 0.20$).²⁸ According to Govindarajan *et al.*, the number of retrieved lymph nodes was not an independent risk factor for disease-specific survival in that study (hazard ratio 0.94, 95% CI 0.88–1.01, $P = 0.09$).²⁷ For the 76 patients in the current study, 9.1 lymph nodes were detected on average, and in 63.2% of patients <12 lymph nodes were harvested. No significance difference was found in OS between the group with <12 or at least 12 lymph nodes (95.3% and 94.1%, respectively, $P = 0.83$). However, DFS was higher in the <12 lymph node group (91.0%) compared to the ≥12 lymph node group (77.6%), even though without a statistically significant difference ($P = 0.63$). This is consistent with the report by Habr-Gam *et al.*²⁸

This study has some limitations. First, this is a single-centre retrospective study with a relatively small sample size. Second, the induction and consolidation chemotherapy in this study was not the standard treatment for locally advanced rectal cancer according to the National Comprehensive Cancer Network or the European Society of Medical Oncology guidelines.^{1,2} However, many clinical studies have already shown that consolidation and induction neoadjuvant chemotherapy can increase the rate of tumour response, which might improve prognosis.^{32–35} Third, the tumour differentiation information was not complete in a substantial part of the included patients and, in addition, the infiltration of lymphocytes

Table 4 Multivariate analysis of OS in patients with ypT0

Variable	Total	Hazard ratio	95% confidence interval	P-value
CEA [†] (ng/mL)		3.38	0.52–22.18	0.20
≤5	54			
>5	22			
Post-operative [‡]		0.39	0.058–2.69	0.34
Chemotherapy	48			
No chemotherapy	28			
ypN		6.11	0.92–40.47	0.06
ypN–	67			
ypN+	9			

[†]CEA before neoadjuvant treatment.

[‡]Post-operative treatment.

CEA, carcinoembryonic antigen; OS, overall survival.

was not assessed during the pathological examination of the specimens.

Conclusion

This study found the prognostic value of elevated serum CEA before NCRT and ypN+ for worse DFS in patients with ypT0. Therefore, radical resection should be considered instead of wait-and-watch approach or 'local resection' in the case of elevated serum CEA before neoadjuvant therapy, even if there is a complete clinical response of the primary tumour after neoadjuvant chemoradiation. For ypT0N+ patients after resection, further studies are needed to determine whether post-operative adjuvant chemotherapy needs to be adjusted to improve long-term prognosis.

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Author Contributions

Hang Zhang: Conceptualization; data curation; formal analysis; methodology; software; writing-original draft; writing-review and editing. **Ge Sun:** Data curation; formal analysis; methodology; writing-review and editing. **Kuo Zheng:** Formal analysis; methodology; software. **Zheng Lou:** Methodology; supervision. **Xian H. Gao:** Methodology; supervision. **Rong G. Meng:** Resources; supervision. **Edgar J. B. Furnée:** Investigation; methodology; supervision; writing-review and editing. **Wei Zhang:** Data curation; funding acquisition; methodology; project administration; supervision.

Conflicts of interest

None declared.

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