Value of ypTNM stage in patients with rectal cancer

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Abstract

Purpose: In the current NCCN guidelines, the prognosis and adjuvant chemotherapy regimen of patients who underwent neoadjuvant chemoradiotherapy, which are based on pre-radiotherapy clinical TNM stage or neoadjuvant pathologic TNM stage, are not clearly described. We investigated neoadjuvant pathologic TNM stage and clinical TNM stage, which can better reflect the prognosis of patients. Moreover, the clinical significance of the adjuvant chemotherapy regimen in different neoadjuvant pathologic TNM stages was studied.

Methods: Between 2010 and 2015, a total of 316 rectal cancer patients who underwent neoadjuvant chemoradiotherapy, followed by radical resection, were retrospectively studied.

Results: Our findings revealed that neoadjuvant pathologic TNM stage was a more important prognostic factor than clinical TNM stage. In different neoadjuvant pathologic TNM stages, adjuvant chemotherapy played important roles in stage-II and -III disease, but played no significant role in pCR and stage-I disease.

Conclusion: Neoadjuvant pathologic TNM stage, rather than clinical TNM stage, was a more important prognostic factor. Among the patients who underwent neoadjuvant chemoradiotherapy, adjuvant chemotherapy had no significant benefit on the survival of patients in terms of pCR and neoadjuvant pathologic TNM stage I, but had different benefits in stage-II and -III disease.

Introduction

The worldwide incidence of colorectal cancer (CRC) is high(Provenzale et al. 2015). In recent years, the prevalence of CRC has been increasing in part because of an aging population. Among the different types of CRC, nearly 50% are rectal cancers(Sung et al. 2021). Many studies have demonstrated that neoadjuvant chemoradiotherapy (nCRT) is effective in reducing local recurrence and preserving the anal sphincter(Rosa et al. 2018; Sauer et al. 2004). Therefore, nCRT has become the standard treatment for locally advanced rectal cancer, according to National Comprehensive Cancer Network (NCCN) guidelines(Benson et al. 2018). However, the response to nCRT varies from pathological complete response (pCR) to disease progression. According to previous studies, approximately 30% of rectal cancer patients who underwent nCRT showed complete response and approximately 60% showed tumor size regression and N stage descension(Goffredo et al. 2021; Ryan et al. 2016; Sun et al. 2016a; Yamashita et al. 2019). Due to individual differences in the response to nCRT, the prognosis of patients might vary greatly. In the current NCCN guidelines, the prognosis and adjuvant chemotherapy regimen of patients with nCRT, which are based on pre-radiotherapy clinical TNM (cTNM) stage or neoadjuvant pathologic TNM (ypTNM) stage, are not clearly described. Therefore, the aim of this study was to investigate cTNM and ypTNM stages, which could better reflect the prognosis of patients with nCRT. Furthermore, we explored the clinical significance of adjuvant chemotherapy in different ypTNM stages.

Materials And Methods

Patients

Between 2010 and 2015, we retrospectively analyzed 316 rectal cancer patients who received nCRT, followed by radical surgery at the Liaoning Cancer Hospital and Institute. Before nCRT, all patients were histologically confirmed to have resectable rectal cancer of clinical T2-4aN0-3M0 stage, according to the 8th edition of the UICC/AJCC TNM classification system. Histological specimens for ypTNM stage were evaluated by two senior pathologists. Patients were excluded if they were diagnosed with unresectable cancer after nCRT, underwent nCRT at other hospitals, died during the peri-operative period, or had incomplete records.

All patients were followed-up for more than 5 years after the surgery. The preoperative staging evaluation included physical and laboratory examinations, enteroscopy with endoscopic ultrasound and pathological biopsy, chest and abdominal computed tomography (CT), and pelvic magnetic resonance imaging (MRI). Most patients were discussed by a multidisciplinary team (MDT) before starting treatment. This study was approved by the Ethics Committee of the Liaoning Cancer Hospital & Institute.

Treatment

All patients were treated with three-dimensional conformal radiotherapy. The standard dose was 50.4 Gy in 1.8-Gy daily fractions. At the same time, capecitabine was mainly used as the chemotherapeutic drug. All patients were reassessed approximately 5 to 6 weeks after treatment with nCRT, before radical surgery was performed. During the period of adjuvant chemotherapy, some patients received mFolfox6, some received capecitabine, and some did not receive chemotherapy.A pCR was defined as the absence of residual tumor in the entire rectal wall and local lymph nodes. Non-pCR was defined as the presence of residual tumor, either in the rectal wall or local lymph nodes.

Follow-up

All patients were followed up by telephone interviews or outpatient visits. Patients were followed-up every 3 to 6 months in the first two years and then once per year. At each follow-up, tests included anal examinations, tumor marker levels, abdomen and lung CT, and/or MRI and colonoscopy, if needed. Overall survival (OS) was defined from the day of the surgery to the death of the patient for any reason.

Statistical analysis

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. The $\chi 2$ test or Fisher's exact test was used to compare categorical variables. The Kaplan–Meier method was used to assess OS. The Cox proportional hazards regression model was used in forward stepwise multivariate survival

analysis. To investigate which TNM stage (cTNM or ypTNM stage) was more important in predicting the prognosis, two-step multivariate survival analysis was used. In step 1 multivariate analysis, all statistically significant prognostic factors from the univariate analysis were included, except for ypTNM stage. In step 2 multivariate analysis, ypTNM stage was also considered, together with cTNM stage and other statistically significant prognostic factors. $P < 0.05$ was considered statistically significance.

Results

Patient characteristics and follow-up

Patient particulars and clinicopathological features are provided in Table 1. A total of 316 patients with rectal cancer who met the criteria were included in the analysis. The median age was 58 years (range, 16–84 years). All patients underwent radical surgery after nCRT. After histopathological examination, 70 patients (22.2%) achieved pCR, and the remaining patients with residual cancer were classified as the non-pCR group (n = 246). Patients with smaller primary tumors and eminence-type cancer were more likely to achieve pCR after nCRT ($P < 0.001$ for all) (Table 1).

Table 1
Clinicopathologic Features of Colorectal Cancer Patient with Neoadjuvant Chemoradiotherapy (n = 316)

Clinicopathologic Features	Total (n = 316)	pCR (n = 70), %	Non-pCR (n = 246), %	P-value
Age (yrs)	173	41(23.7%)	132(76.3%)	0.466
< 60	143	29(20.3%)	114(79.7%)	
≥ 60				
Sex	219	42(19.2%)	177(80.8%)	0.056
Male	97	28(28.9%)	69(71.1%)	
Female				
Primary tumor Diameter	170	53(31.2%)	117(68.8%)	0.000
<3 cm	146	17(11.6%)	129(88.4%)	
≥3 cm				
Macroscopic type	65	41(63.1%)	24(36.9%)	0.000
Exophytic type	251	29(11.6%)	222(88.4%)	
Ulcerative type				
Histological differentiation	276	62(22.4%)	214(77.6%)	0.726
Well to moderately	40	8(20.0%)	32(80.0%)	
Poorly				

The median follow-up time was 47 months (range, 12–101 months) for the 316 rectal cancer patients. At the time of the last follow-up, 73 patients (23.1%) had died due to tumor progression and all patients experienced recurrence: five patients (1.6%) in the pCR group and 68 patients (21.5%) in the non-pCR group. One patient died due to an accident. The 5-year OS was 91.5% in the pCR group and 64.1% in the non-pCR group. The OS of the pCR group was better than that of the non-pCR group (P < 0.001) (Fig. 1).

Prognostic Features Of Ncrt Patients

Univariate and/or multivariate analyses of the prognostic factors in pCR and non-pCR groups are provided in Tables 2 and 3, respectively. Univariate analyses showed that primary tumor diameter (P = 0.023), clinical N (cN) stage (P = 0.015), and cTNM stage (P = 0.051) entered into multivariate analysis in the pCR group. Moreover, multivariate analysis demonstrated that cN stage was the only significant independent factor (HR = 6.917; P = 0.038). For the non-pCR group, histologic grade (P = 0.052), cTNM stage (P = 0.021), and ypTNM stage (P < 0.001) were associated with the prognosis of patients who underwent nCRT. To determine which factor (histologic grade, cTNM stage, or ypTNM stage) was the most important in predicting the prognosis, two-step multivariate analysis was applied (Table 4). In step

1, the significant factors (histologic grade and cTNM stage) from the univariate analysis were considered, except for ypTNM stage, and cTNM stage was confirmed to be an independent factor in predicting a better prognosis. In step 2, when ypTNM stage was considered, ypTNM stage rather than cTNM stage became the most important prognostic factor. In other words, ypTNM stage was a more important prognostic factor than cTNM stage.

Table 2
Univariate and Multivariate Prognostic Analysis for pCR Patients with Colorectal Cancer (n = 70)

Clinicopathologic Features	n	Univariate		Multivariate	
		Overall survival time (months)	P-value	Hazard ratio (95% CI)	P-value
Age (yrs)	41	82.150	0.993		
< 60	29	75.984			
≥ 60					
Sex	42	80.893	0.335		
Male	28	77.524			
Female					
Primary tumor Diameter	53	84.190	0.023		0.076
<3cm	17	69.177			
≥3cm					
Macroscopic type	41	78.724	0.426		
Exophytic type	29	80.521			
Ulcerative type					
Histological differentiation	8	82.542	0.594		
Well to moderately	62	76.286			
Poorly					
Clinical T stage	20	78.989	0.191		
T1-T2	50	77.142			
T3-T4					
Clinical N stage	51	84.219	0.015	6.917(1.133–42.216)	0.038
N0	19	66.372			
N+					
Clinical TNM stage	18	83.765	0.051		0.721
I	33	77.724			
II	19	66.372			
III					

Table 3
Univariate Prognostic Analysis for Non-pCR Patients with Colorectal Cancer (n = 246)

Clinicopathologic Features	n	Overall survival time (months)	P-value
Age (yrs)	132	74.011	0.171
< 60	114	80.128	
≥ 60			
Sex	177	75.678	0.826
Male	69	76.750	
Female			
Primary tumor Diameter	117	79.660	0.348
<3cm	129	73.468	
≥3cm			
Macroscopic type	222	82.127	0.422
Exophytic type	24	76.371	
Ulcerative type			
Histological differentiation	214	78.640	0.052
Well to moderately	32	61.970	
Poorly			
Clinical TNM stage	102	81.106	0.021
II	144	72.517	
III			
Neoadjuvant pathologic TNM stage	51	93.274	0.000
I	94	79.839	
II	101	63.715	
III			

Table 4
Two-Step Multivariate Analysis of the Prognostic Factors for Non-pCR Patients with Colorectal Cancer

	Hazard ratio	95% CI	P
Step 1	1.811	1.084–3.025	0.069
Histological differentiation			0.023
Clinical TNM stage			
Step 2	2.704	1.811–4.038	0.244
Histological differentiation			0.974
Clinical TNM stage			0.000
Neoadjuvant pathologic TNM stage			
Step 1, with consideration of all significantly important prognostic factors in univariate analysis except for neoadjuvant pathologic TNM stage after surgery.			
Step 2, with consideration of all significantly important prognostic factors in univariate analysis including neoadjuvant pathologic TNM stage after surgery.			

Adjuvant Chemotherapy For Ncrt Patients

Due to the important role of ypTNM stage in the prognosis of patients, we divided patients into three groups to study the clinical significance of the adjuvant chemotherapy regimen in different ypTNM stages. Among 316 patients, 155 patients received mFolfox6 adjuvant chemotherapy, 96 patients received capecitabine adjuvant chemotherapy, and 65 patients received no chemotherapy. In the pCR + ypTNM stage I group, there were no significant differences in the survival of patients who received mFolfox6, capecitabine, and no chemotherapy (Fig. 2). In the ypTNM stage II group, there were significant differences in the survival of patients who received mFolfox6 versus no chemotherapy, with 5-year OS rates of 71.3% versus 48.7% (P = 0.032), and no significant differences in the survival of patients who received mFolfox6 versus capecitabine and capecitabine versus no chemotherapy (Fig. 3). In the ypTNM stage III group, there were significant differences in the survival of patients who received mFolfox6 versus capecitabine and mFolfox6 versus no chemotherapy, with 5-year OS rates of 57.0% versus 55.0% (P = 0.020) and 57.0% versus 32.1% (P = 0.025), respectively. There was no significant difference in the survival of patients who received capecitabine versus no chemotherapy (Fig. 4).

Discussion

The current NCCN guidelines fail to clearly describe that the adjuvant treatment and prognosis of rectal cancer after surgery are based on pre-radiotherapy cTNM stage or ypTNM stage. In this study, we found that ypTNM stage was a more accurate factor to reflect the prognosis of rectal cancer patients who

underwent nCRT. In the pCR group, cN stage was the most important independent prognostic factor. In the non-pCR group, however, ypTNM stage was a more important prognostic factor than cTNM stage. Many studies have also reported the importance of the neoadjuvant pathological stage in the prognosis of patients. Sun et al.(Sun et al. 2016b) investigated 317 rectal cancer patients who underwent radical surgical resection following nCRT and observed that ypTNM stage was the only independent risk factor in these patients. Similarly, Kim et al.(Kim et al. 2016) reported that ypTNM stage was an important prognostic factor in the prediction of local recurrence and distant metastasis in rectal cancer patients. Jang et al.(Jang et al. 2012) studied 830 patients with rectal cancer who underwent nCRT and reported that the residual tumor cells in local lymph nodes were risk factors for distant metastasis. Moreover, Kim et al.(Kim et al. 2008) reported that ypN + stage and lateral lymph node size were risk factors for recurrence in the lateral pelvis. Therefore, we concluded that ypTNM stage might better reflect the prognosis of patients than cTNM stage. Furthermore, we speculated that the patients who were sensitive to nCRT might have a better prognosis.

Rectal cancer is often reduced to different degrees after nCRT, although some patients achieve pCR, which brings much controversy to the use of adjuvant chemotherapy. Sun et al.(Zhifei et al. 2017) retrospectively studied 12696 patients in the National Cancer Database and observed that adjuvant chemotherapy among patients with rectal cancer who underwent nCRT conferred a survival benefit. On the contrary, Baird et al.(Baird et al. 2017) found no significant difference in survival or disease recurrence between patients who received adjuvant chemotherapy and patients who did not. We believe that the opposite conclusions might be due to differences in the composition of patients between the two studies. In the following studies, patients were stratified according to stage. Hu et al.(Xiang et al. 2019) reported that patients with ypTis-2N0 rectal cancer did not benefit from adjuvant chemotherapy after nCRT, while Maas et al.(Maas et al. 2015) systematically analyzed 13 databases of neoadjuvant radiotherapy for rectal cancer and concluded that postoperative adjuvant chemotherapy did not benefit patients with pCR. However, some contrary studies showed that adjuvant chemotherapy is effective for early-stage cancer patients who underwent nCRT(Sven et al. 2017; Turner Megan et al. 2019). Although there are different conclusions, most studies believe that adjuvant chemotherapy is still necessary for patients with advanced- stage disease, which is similar to our result. A multicenter randomized controlled clinical study conducted in Asia confirmed that oxaliplatin + 5-FU combination chemotherapy can significantly improve the 3-year disease-free survival of patients with ypTNM stage III rectal cancer compared with 5-FU chemotherapy alone, but it has no effect on the prognosis of patients with ypTNM stage II rectal cancer(Hong et al. 2014). You et al.(You et al. 2014) performed a retrospective study of 160 rectal cancer patients and observed that adjuvant chemotherapy might not improve the survival of ypT0-2N0 patients but might be meaningful for ypT3-4N0 patients in terms of the 5-year OS.

In our analysis, we concluded that adjuvant chemotherapy had no significant effect on the prognosis of patients who had descending stage-to-pCR and ypTNM stage I rectal cancer, regardless of the stage before treatment. Therefore, we believe that adjuvant chemotherapy is unnecessary for patients in pCR, as well as for those with ypTNM stage I rectal cancer. Liao et al.(Liao et al. 2021) also reported that adjuvant chemotherapy is not required for patients with ypT0-2N0 rectal cancer down-staged by nCRT,

which was consistent with our findings. In the analysis of adjuvant chemotherapy in patients with ypTNM stage II rectal cancer, we found that the prognosis of patients who received mFolfox6 was significantly better than that of patients who received no chemotherapy. However, the prognosis of patients who received capecitabine was similar to those who received mFolfox6. This finding shows that mFolfox6 adjuvant chemotherapy is the best choice for patients with ypTNM stage II rectal cancer, but capecitabine might also be an option. Moreover, in the analysis of patients with ypTNM stage III rectal cancer, we found that the prognosis of patients who received mFolfox6 was significantly better than that of patients who received capecitabine or no chemotherapy. However, the prognosis of patients who received capecitabine was similar to those who received no chemotherapy. This finding shows that mFolfox6 adjuvant chemotherapy is the best choice for patients with ypTNM stage III rectal cancer, rather than capecitabine and no chemotherapy. This conclusion was similar to that of Hong and colleagues(Hong et al. 2014). In summary, adjuvant chemotherapy might not be necessary in early-stage rectal cancer patients with pCR and ypTNM stage I who achieved good effects in nCRT. For patients with advanced-stage disease, the intensity of the adjuvant chemotherapy might need to be strengthened with the increase of ypTNM stage.

The main strength of our study is that all patients were stratified according to ypTNM stage. Therefore, we could systematically analyze the clinical significance of the adjuvant therapy regimen in different stages, while avoiding the impact of the different stages on survival. However, there are several limitations in the current study. First, the sample size was relatively small, especially when stratified by ypTNM stage, which contributed to the low statistical power of the prognostic comparisons. Second, because of the nature of retrospective studies, selectivity bias was inevitable. Therefore, further studies should be carried out to confirm our results.

In conclusion, our study offers two important conclusions. First, it concluded that ypTNM stage was better than cTNM stage in predicting the prognosis of patients, which is not clearly pointed out in the current NCCN guidelines. Second, due to the importance of ypTNM stage in the prognosis of patients with nCRT, we stratified patients according to this parameter and analyzed the impact of adjuvant chemotherapy on the prognosis of patients. Adjuvant chemotherapy might not be necessary for patients with pCR and ypTNM stage I who achieved good effects in nCRT, and for patients with advanced-stage disease, the intensity of adjuvant chemotherapy might need to be strengthened with the increase of ypTNM stage. This study provides evidence for the implementation of more accurate adjuvant therapy after nCRT. To further the findings of this study, we are currently conducting a large multicenter retrospective study.

Declarations

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Availability of data and materials: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Yue Chen collected documents and wrote the paper. Deyu Sun and Zhe Sun managed the design and modified the paper. Xinxin Dong and Fang Liu collected documents and assisted in writing discussion section.

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Figures

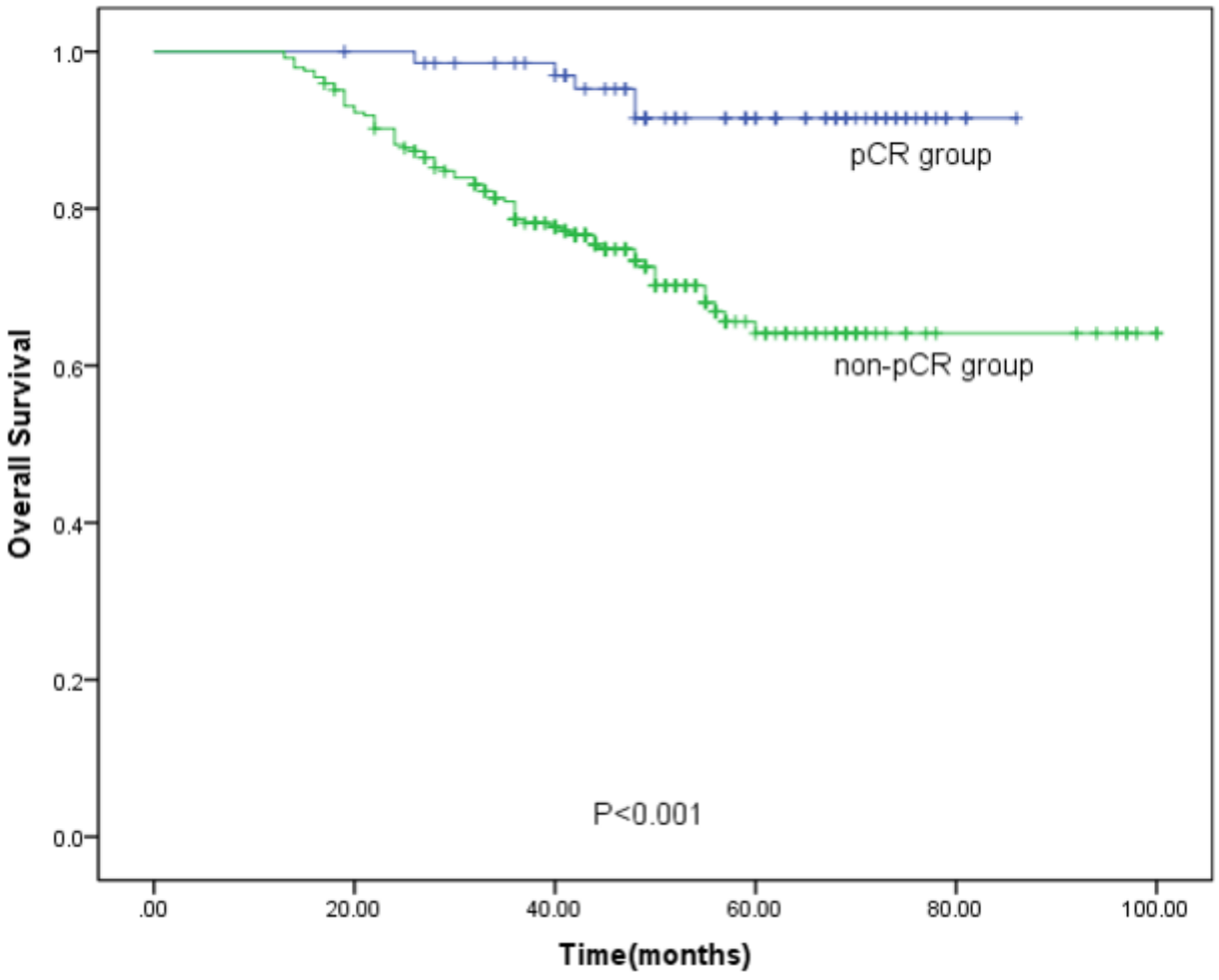

Figure 1

Prognostic analysis of pCR and non-pCR group. There was significant difference between two groups (P<0.001).

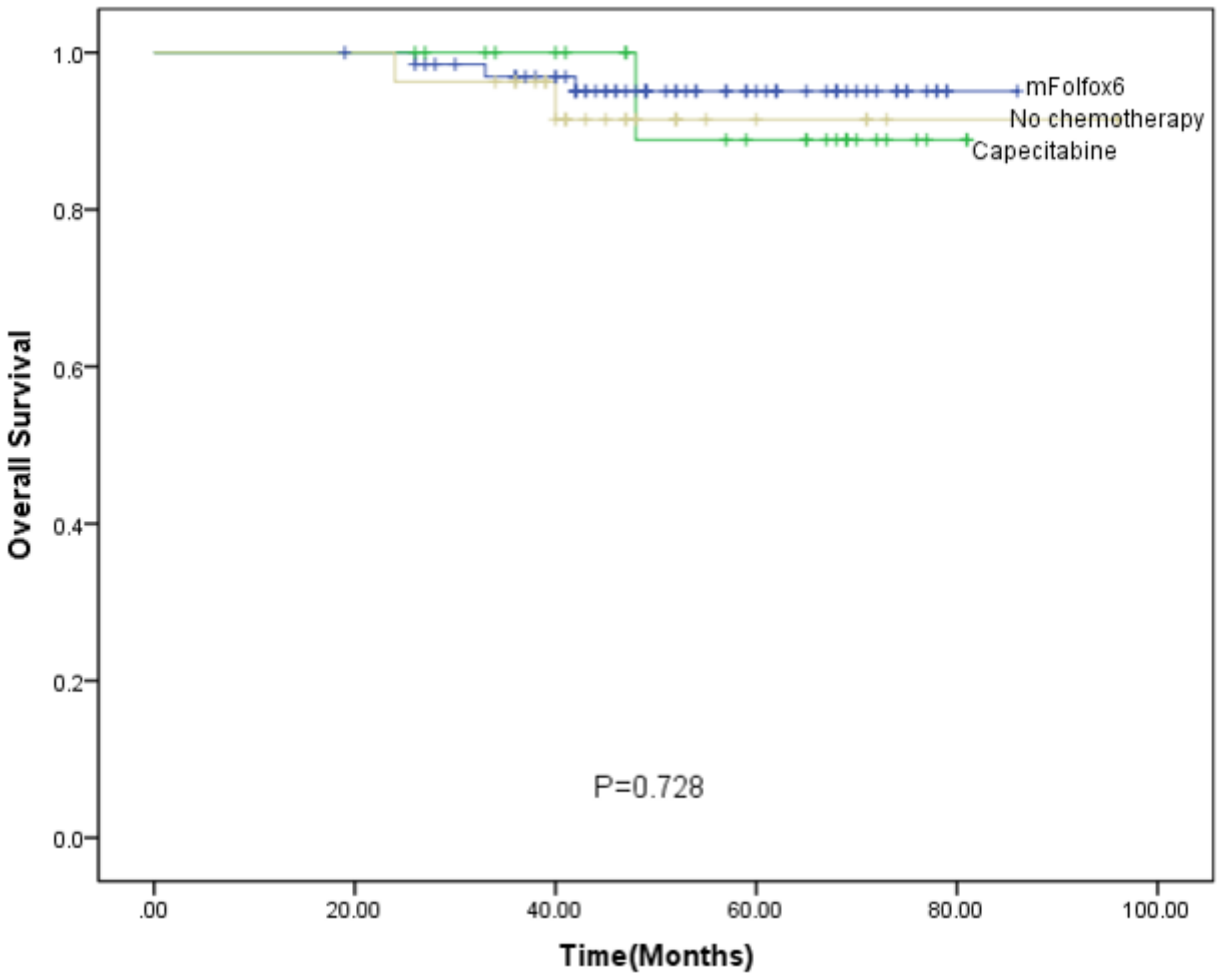

Figure 2

Prognostic analysis of mFolfox6, Capecitabine and No chemotherapy patients with different adjuvant chemotherapy in pCR and ypTNM I group. There were no significant differences between three groups (P=0.728).

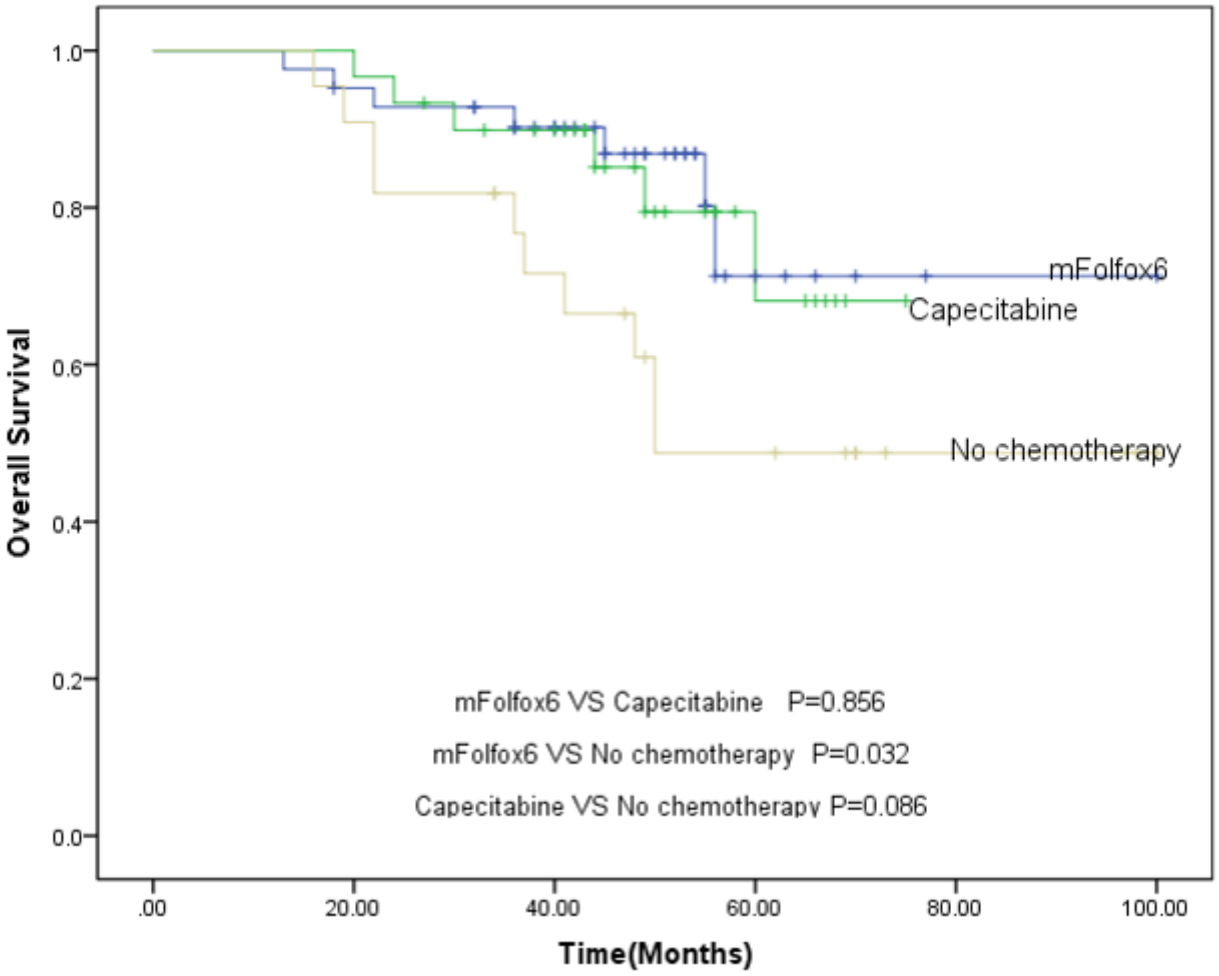

Figure 3

Prognostic analysis of mFolfox6, Capecitabine and No chemotherapy patients with different adjuvant chemotherapy in ypTNM II group. There were significant differences between mFolfox6 and No chemotherapy (P=0.032) and no significant differences in mFolfox6 VS Capecitabine (P=0.856) and Capecitabine VS No chemotherapy (P=0.086).

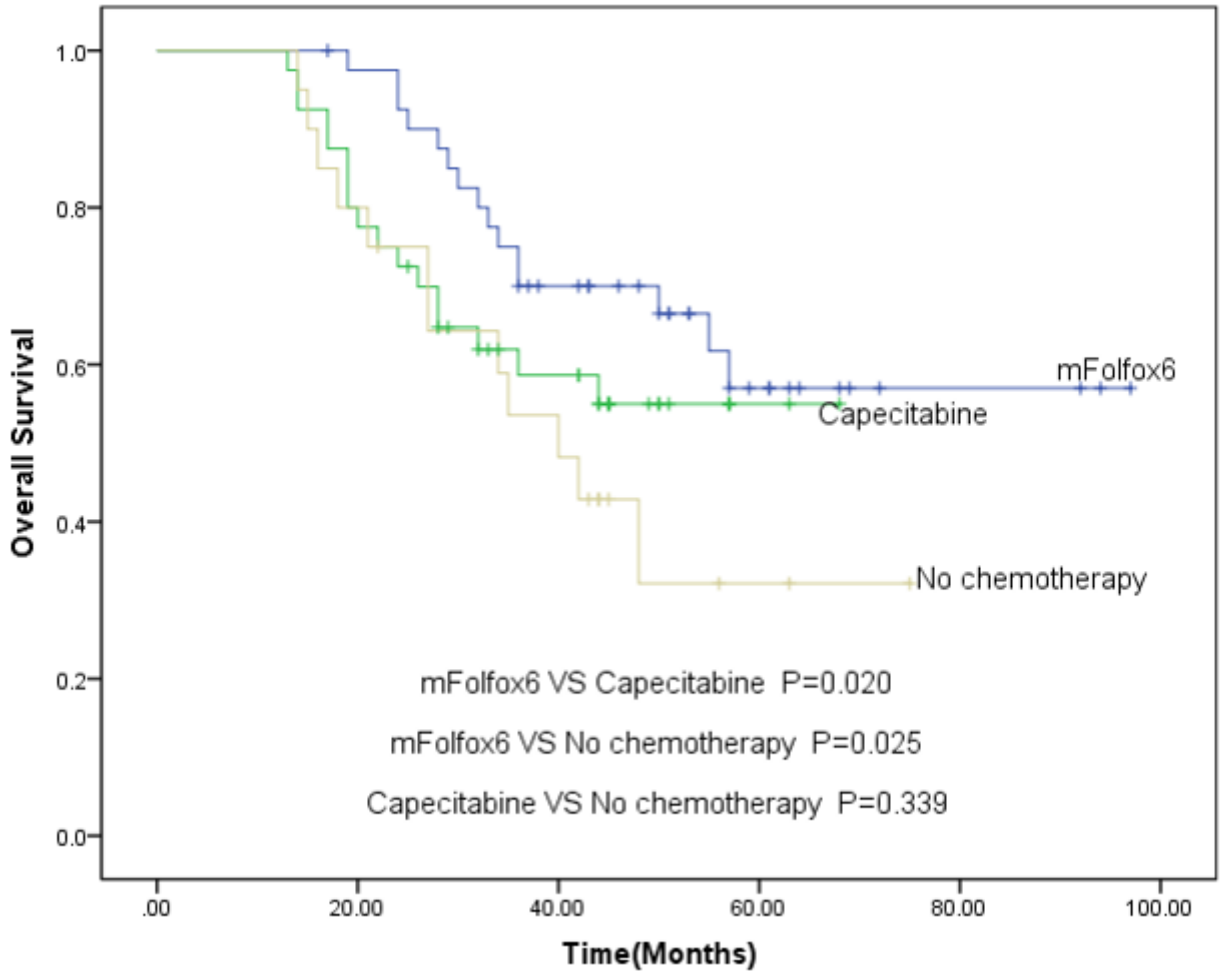

Figure 4

Prognostic analysis of mFolfox6, Capecitabine and No chemotherapy patients with different adjuvant chemotherapy in ypTNM III group. There were significant differences in mFolfox6 VS Capecitabine (P=0.020) and mFolfox6 VS No chemotherapy (P=0.025) and no significant difference between Capecitabine and No chemotherapy (P=0.339).