Locally Advanced Rectal Cancer Patients Got PCR After Chemoradiotherapy May Have Better Survival Outcomes: A Retrospective Analysis of 246 Patients.

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Research Article

Keywords: Rectal cancer, neo-adjuvant chemoradiotherapy, pathological complete response, survival

Posted Date: November 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1023449/v1

Abstract

Objective: To investigate whether the locally advanced rectal cancer patients who got a pathological complete response after neo-adjuvant chemoradiotherapy have a better survival.

Methods: From January 1 2014 to January 1 2018, the clinical information of locally advanced rectal cancer patients who underwent neo-adjuvant chemoradiotherapy were collected for a retrospective analysis. Then a telephone follow-up visit was done to get the patients' survival information of progression-free survival and overall survival. At last the information was analyzed by Kaplan-Meier analysis, log-rank test and cox-regression analysis.

Results: The clinical information of 246 locally advanced rectal cancer patients were collected and analyzed, which shows that the PCR rate after chemoradiotherapy was 20.3% in these patients. There were correlations between pathological grade(grade III-IV Vs. I-II, *P*=0.001), CRM invasion(positive Vs. negative, *P*=0.001), clinical T stage(T4 Vs. T1-3, *P*=0.000), PCR status(PCR Vs. Non-PCR, *P*=0.027), downstage after preoperative therapy(yes Vs. not, *P*=0.009) and PFS. Similarly, age(≤60 Vs. >60, *P*=0.000), pathological grade(grade III-IV Vs. I-II, *P*=0.016), EMVI status(positive Vs. negative, *P*=0.005), CRM invasion(positive Vs. negative, *P*=0.000), clinical T stage(T4 Vs. T1-3, *P*=0.000), clinical N stage(N0-1 Vs. N2, *P*=0.013), PCR status(PCR Vs. Non-PCR, *P*=0.010), downstage after preoperative therapy(yes Vs. not, *P*=0.002) were associated with the OS. After the Cox-regression analyses, the responses after preoperative therapy or T4 tumors were identified as the prognostic factors that affected PFS and OS.

Conclusions: The PCR rate after chemoradiotherapy was 20.3% in locally advanced rectal patients. Stage T1-3, better response after chemoradiotherapy tumors (PCR or downstage) might have a better survival outcome.

0. Introduction

Currently, the standard treatment for middle-low locally advanced rectal cancer is neo-adjuvant chemoradiotherapy followed by curative surgical resection according to the guidelines of both the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) [1-3] . After the neo-adjuvant chemoradiotherapy, about 70% patients got a substantial tumor downstage , and about 15 to 20% of these cases got a pathological complete remission (PCR), which was defined as no tumour cells can be found after full pathologic examination of the resected specimen (the stage was ypT0N0), which is defined as stage 0 disease [3,4]. For these PCR patients, some authors suggested that it is need to reconsider the urgency of surgical resection[4]. Up to now, there's not any standard suggestion for a complete remission (clinical, biological or radiological) has been established in all the literature and guidelines, and total mesorectal excision (TME) remains the standard treatment for these patients. In the meantime, there were a lot of previous researches suggested that patients with ypT0N0 stage may have better prognoses, including improved overall survival and disease-free survival (DFS) compared to the other stages. However, whether the PCR patients have a better survival outcome is still controversial [4-

[8]. What' more, the specific prognostic factors for these patients are still unclear. The aim of this study was to evaluate the long-term oncologic outcomes and predictive factors for survival after a PCR of middle-low rectal cancer.

1. Patients And Methods

1.1 Patients

This retrospective analysis was carried out in 2020, when the inpatient records of locally advanced rectal cancer patients who treated with preoperative chemoradiotherapy in the first affiliated hospital of Kunming medical university were screened from January 1, 2014 to December 31, 2019 and the patients' information including identity number, name, age, gender, ECOG PS , telephone number, clinical TNM stage, tumor location, histology, MRI information (including cTNM stage, CRM, EMVI) and survival information were obtained and analyzed. For there was not any obtained data could identify the involved patient, the data collecting and the follow-up were approved by the ethics committee of the first affiliated hospital of Kunming medical university .

1.1.1 Inclusion criteria

Patients aged from 18-80 years; ECOG 0-2; proved to be middle-low rectum adenocarcinoma; with clinical stage T3-4 or $T_{any}N+$(International Union Against Cancer, version 8); without other fatal diseases like severe cardiac or pulmonary diseases; without previously treatment; treated with preoperative concurrent chemoradiotherapy and radical operation 8-12 weeks later; with normal liver, renal and bone marrow function and complete follow-up information.were included.

1.1.2 Exclusion criteria

Patients younger than 18 or older than 80; ECOG ≥3; without histology information, with severe diseases of cardiac, respiratory or other system; with abnormal liver, renal or bone marrow function; without complete chemoradiotherapy; without sequential operation or without complete follow-up information were excluded.

1.2 Treatment

The chemotherapy regimen was separately to administer Capecitabine(Xeloda, Roche) orally, (825mg/m^2, twice a day, half an hour after diet, from Monday to Friday during radiotherapy), the radiotherapy was using IMRT technology and as to the clinical target volume, it was defined as the upper boundary was the lower edge of the L5 vertebral body, and the lower boundary was the lower edge of the tumor (3cm), including the anterior sacral soft tissue, drainage area of the internal iliac lymph node and the mesenteric region. Besides, according to the invasion and lymph node metastasis of the tumor, the external iliac, inguinal and common iliac lymph node regions were included if necessary, the important organs, such as small intestine, bladder and femoral head, were delineated and the total dose was 45-50.4Gy, 1.8-2.0Gy/

fraction, 5 fractions/week, and continued radiotherapy for 5-6 weeks. All the treatment including the chemoradiotherapy, and the subsequent therapy were performed according to the guidelines, such as the NCCN and ESMO guidelines.

Adverse effects were observed and graded according to the Common Terminology Criteria for Adverse Events (version 3.0), severe events were treated according to the clinical guidelines like NCCN guidelines, and the dose of capecitabine or radiotherapy could be adjusted by physicians according to the adverse effects if necessary. Subsequently, post-study treatment was given at the discretion of the physician and patient according to the guidelines.

1.3 Follow-up and Assessments

All enrolled patients' information were gotten from the inpatient record system, all the selected patients were followed up by telephone for PFS, OS, responses and adverse events, and tumors assessments were performed via pathological information of operation and magnetic resonance imaging(MRI), confirmed through reviewing the data from picture archiving and communication system(PACS) and the hospital information system(HIS) by two experienced pathologists or radiologists, Among that, PFS was defined as the time from treatment beginning to the earliest occurrence of disease progression or death from any cause, especially, the data of patients who had not experienced progression or died at data cutoff would be censored at the last tumor assessment, while OS was assessed from the date of treatment beginning to the date of death as the result of any cause, or data were censored at the last date that the patient was confirmed to be alive. Tumor response according to RECIST 1.1 was assessed at baseline and 8 weeks after chemoradiotherapy. The process was similar to another research of us which was published on September 2015.[9]

1.4 Statistical Analysis

The primary end points were PFS and OS between PCR and non-PCR patients. single factor analysis for which were performed to explore the potential differences between groups with age (≤60 vs. >60), gender (male vs. female), PS (0-1 vs. 2), clinical T stage (T1-3 vs. T4), clinical N stage(N0-1 vs. N2) ,CRM invasion(CRM+ vs. CRM-), EMVI(EMVI+ vs. EMVI-), treatment reaction(downstage vs. not) by Kaplan-Meier survival analysis and log-rank test. Then, the cox-regression analysis were done to identify the interested factors and adjust the infection of the other confounding factors to the interested factors. Finally, statistical analyses were performed via using IBM ® SPSS® version 19.0.

2. Results

2.1 Patients

From January 1, 2014 to December 31, 2019, 387 rectal cancers patients were eligible from the inpatient record data base of the First Affiliated hospital of Kunming Medical University by screening "rectal cancer", "preoperative chemoradiotherapy" and "operation". After meeting the settings of inclusion criteria

and exclusion criteria, 141 patients were excluded (17 were excluded for age, 42 didn't accepted radical operation, 34 had systematic disease that may affect the results, 27 couldn't acquire the preoperative pathological specimens or radiologic images and 21 had not complete the preoperative chemoradiotherapy) and 246 patients were enrolled(Figure 1), where all enrolled 246 patients aged from 26 years old to 78 years old (median 61), and the median follow-up time was 49.0 months (ranged from 18.0-70.5 months). The baseline characteristics (age, sex, pathological grading, EMVI,CRM, clinical T stage, clinical N stage, pathological T stage, pathological N stage, PCR status and down-stage status) were as follow in Table 1.

2.2 Pfs, Os And The Associated Factors

Kaplan-Meier survival analysis and log-rank test were done to detect the correlation between the single factor and PFS or OS. As a result, there were no correlations between age, sex, EMVI status, clinical N stage and PFS, the log-rank *P* were 0.061, 0.665, 0.856 and 0.252, respectively. Conversely, there were correlations between pathological grade(grade III-IV Vs. I-II, *P*=0.001), CRM invasion(positive Vs. negative,*P*=0.001), clinical T stage(T4 Vs. T1-3, *P*=0.000), PCR status(PCR Vs. Non-PCR, *P*=0.027), downstage after preoperative therapy (yes Vs. not, *P*=0.009) and PFS. Patients with pathological grade I-II, CRM not invaded, clinical T1-3, got PCR or downstage after preoperative chemoradiotherapy may have a better PFS. (Table 2 ,Figure 2)

At the same time, there were no correlation between sex (*P*=0.565) and OS. Oppositely, age(≤60 Vs. >60, *P*=0.000), pathological grade(grade III-IV Vs. I-II, *P*=0.016), EMVI status(positive Vs. negative, *P*=0.005), CRM invasion(positive Vs. negative, *P*=0.000), clinical T stage(T4 Vs. T1-3, *P*=0.000), clinical N stage(N0-1 Vs. N2, *P*=0.013), PCR status(PCR Vs. Non-PCR, *P*=0.010), downstage after preoperative therapy(yes Vs. not, *P*=0.002) were associated with the OS, younger than 60 years, grade I-II, EMVI negative, CRM negative, clinical T1-3, clinical N0, PCR or downstage after preoperative therapy seemed to have a better survival outcome. (Table 2 ,Figure 3)

Cox-regression analyses were done to identify all the factors that may associate with survival. Clinical T stage(*P*=0.000, OR=32.761, 95%CI, [11.25-95.40]) and PCR after preoperative chemoradiotherpay(*P*=0.009, OR=32.761, 95%CI, [11.25-95.40]) were testified to be related to PFS, where the T4 and non-PCR patients had a higher risk to progression. Similarly, clinical T stage(*P*=0.000, OR=81.426, 95%CI, [39.378-120.138]), PCR(*P*=0.001, OR=22.030, 95%CI, [16.022-38.625]) and downstage (*P*=0.009, OR=20.188, 95%CI, [2.088-195.233]) after preoperative chemoradiotherpay were testified to be associated with OS. In the meantime, the T4, non-PCR and not downstage patients would have a higher risk to death.

3. Discussion

This study was designed to investigate that whether the middle-low rectal cancer patients who got a pathological complete response after neoadjuvant cheomradiotherapy followed by TME would have a

better survival outcome. According to our study, there were totally two findings, namely the PCR rate of the 246 patients was 20.3%(50/246), which is similar to someone else's previous studies[10–13], as well as patients with pathological grade I-II, CRM not invaded, clinical T1-3, got PCR or downstage after preoperative chemoradiotherapy may have a better PFS and patients younger than 60 years, grade I-II, EMVI negative, CRM invasion negative, clinical T1-3, clinical N0, PCR or downstage after preoperative therapy seemed to have a better OS by single factor Kaplan-Meier survival analysis and log-rank test. After excluding the interaction effect of all the factors by cox-regression analysis, clinical T stage and PCR were the factors that related to PFS, clinical T stage, PCR and downstage after preoperative chemoradiotherapy were the factors that associated with OS, and clinical T1-3, got PCR or downstage after preoperative chemoradiotherapy may have a better survival.

Increasing evidence and accumulating data indicate that T4 might have a worse outcome than that of T1-3 disease, which means that within T4 diseases, there would be a wider invasion of visceral peritoneum or pelvic organs (like the bladder, uterus, prostate gland or the cervix), more chances to invade the blood vessels, lymph-vessels or the nerves, and more possibly to metastasize[14–15] compared with T1-3 diseases. Worstly, if the tumor has locally or distant metastasis, the survival outcome would become poorer., where several studies have supported this theory already.

Treatment responses might be another factor that affect the survival outcome. Tumors that were sensitive to preoperative chemoradiotherapy, such as PCR or downstage tumors, seemed like having a better survival[16–19] and the reasons for this were as follow. Firstly, sensitive tumors were likely to have smaller tumor volume, less invasion of blood vessels or lymph vessels and less possibility to metastasize. Secondly, sensitive tumors were easily to be eliminated by the chemotherapy or radiotherapy. At last, the sensitive tumors might have more chances to receive radical operation and have a relatively less surgical damage, which might affect the survival.

Certainly, there were some inadequacies in our study when discussing our study results, including the retrospective study setting, short follow-up period, small sample size and the potential bias inherent in the data collection and statistic analysis. We realize that limitations in the perioperative evaluations may exist, such as the lack of face-to-face follow-up, systematic post-CRT MRI examinations for some patients were not found, differences in radiotherapy target volume contouring between physicians, and difficulties in the pathological analysis for the specimens when the TRG grading. However, extremely specific attention was focused on all specimens of the patients that got a PCR, and the specimens were reviewed by a second pathologist to confirm. To our knowledge, this is the first study to indicate that T1-3 tumors, pCR or downstage after chemoradiotherapy were associated with better survival outcome for rectal cancer, which was still encouraging, it was worthy of further investigation.

4. Conclusion

In our study, PCR rate after chemoradiotherapy was 20.3% in locally advanced rectal patients. Stage T1-3, better response after chemoradiotherapy(pCR or downstage) tumors might have a better survival

outcome.

Declarations

Declaration of competing interest

There is no conflict of interest. The study was funded by scientific research fund of Yunnan Education Department (No.2020J0162).

Ethical Statement

This retrospective study is involved in patients' personal information ,when the data collecting of these patients , the protocol received approval of the Ethics Committee of the First affiliated hospital of Kunming medical university.

Informed consent

Identifying details of the participants are not contained in this paper. All collected information is anonymized and the submission does not include images that may identify the patient. Informed consent was waived by the ethics committee of the first affiliated hospital of Kunming medical university.

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Tables

Tab 1. The baseline characteristics of enrolled patients

		N(%)		Median	Range
		N	%		
Age group	≤60	119	48.4		
	>60	127	51.6		
Sex	male	160	65.0		
	female	86	35.0		
Pathological grading	I-II	177	72.0		
	III-IV	69	28.0		
EMVI	positive	161	65.4		
	Negative	85	35.6		
CRM invasion	positive	125	50.8		
	Negative	121	49.2		
Clinical T	1-3	187	76.0		
	4	59	24.0		
Clinical N	0	83	33.7		
	1-2	163	66.3		
PCR status	yes	50	20.3		
	no	196	79.7		
Down stage after preoperative therapy	yes	190	77.2		
	no	56	22.8		
Age(year)				61	26-78
Follow up time(month)				49.0	18-70.5

Tab 2. The Single factor analysis for PFS and OS

		PFS	OS
		Log-rank *P* Value	Log-rank *P* Value
Age group	≤60	0.061	0.000
	>60		
Sex	male	0.665	0.565
	female		
Pathological grading	I-II	0.001	0.016
	III-IV		
EMVI	positive	0.856	0.005
	Negative		
CRM invasion	positive	0.001	0.000
	Negative		
Clinical T stage	1-3	0.000	0.000
	4		
Clinical N stage	0	0.252	0.013
	1-2		
PCR status	yes	0.027	0.010
	no		
Down stage after preoperative therapy	yes	0.009	0.002
	no		

Figures

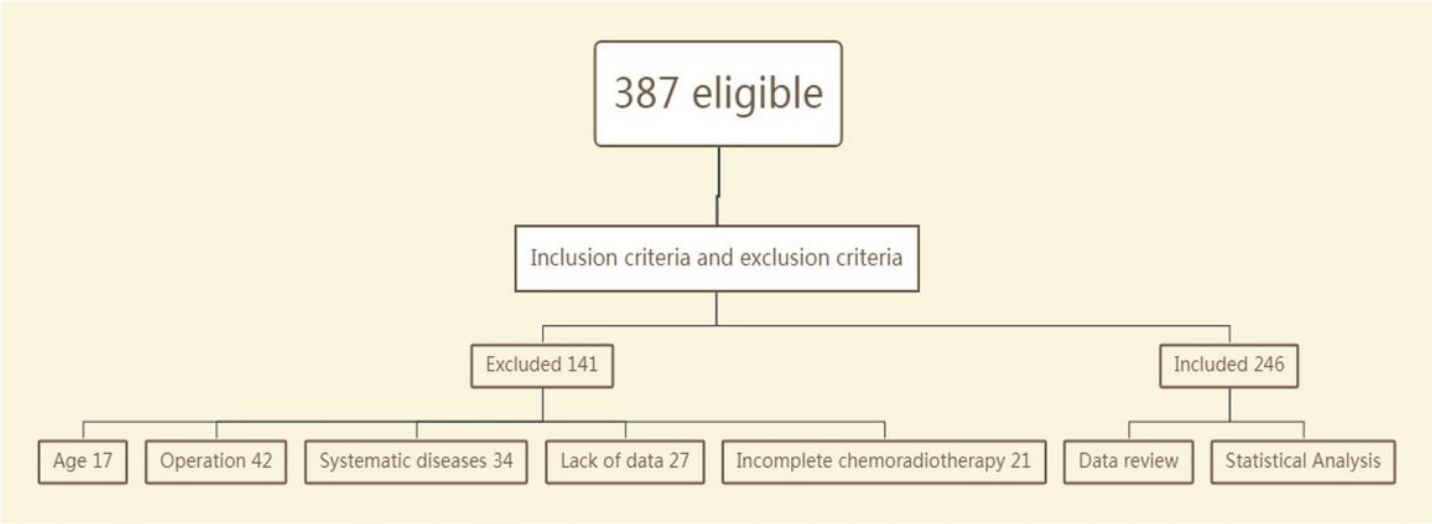

Figure 1

Patients meet the inclusion and exclusion criteria

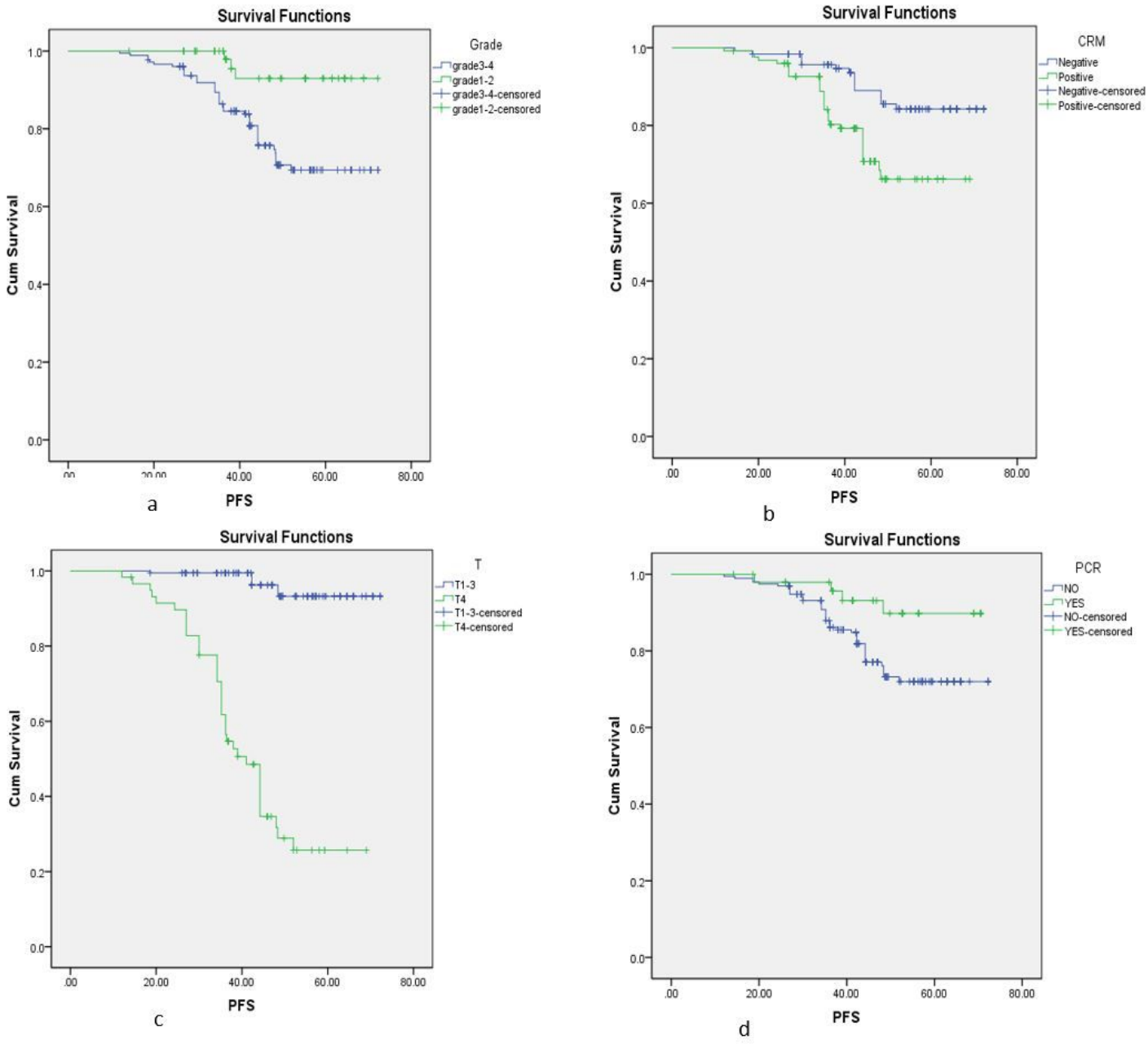

Figure 2

Pathological grade 1-2(a), CRM Negative (b) T1-3(c) or PCR(d) patients have a better PFS

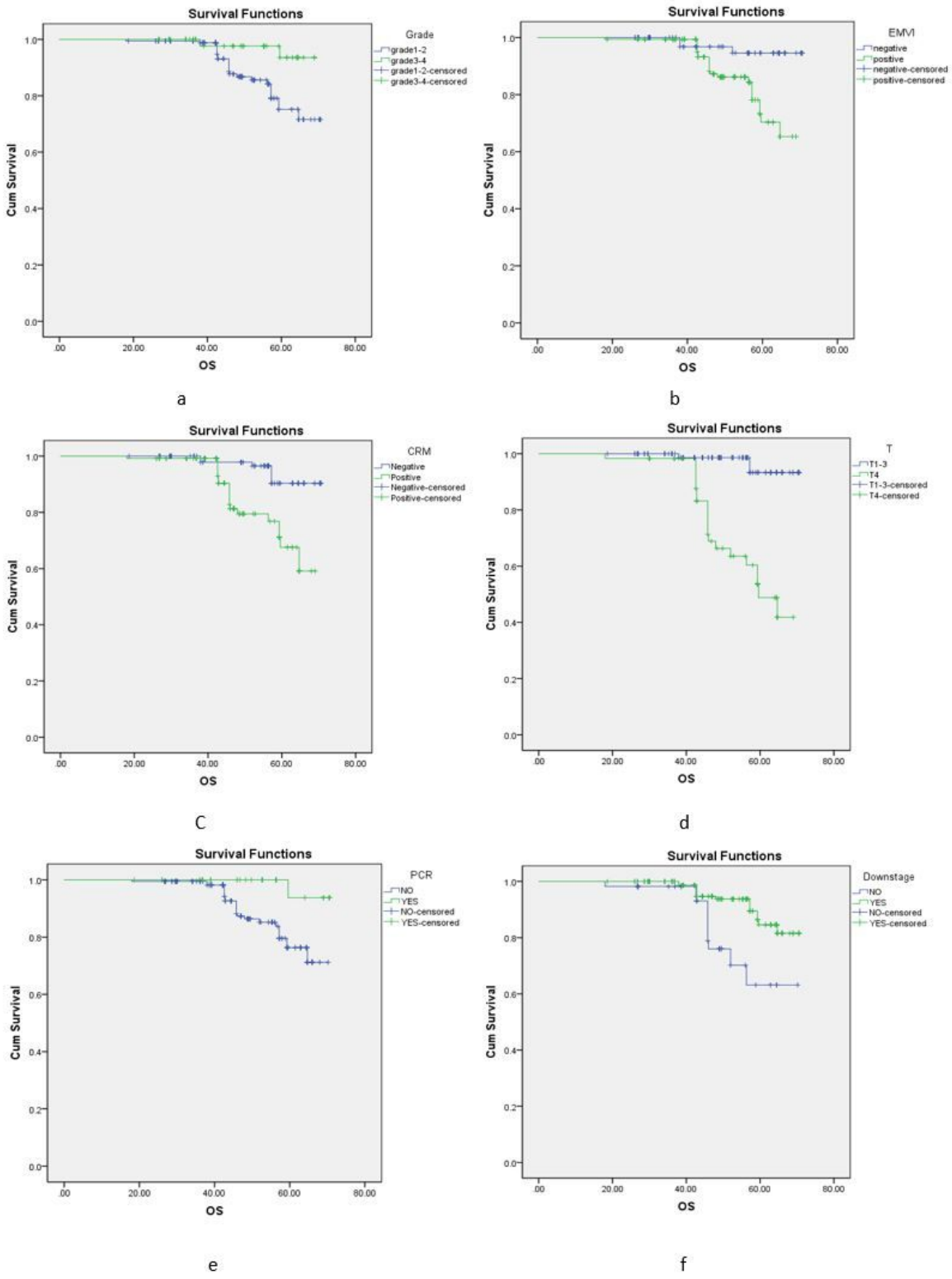

Figure 3

Pathological grade 1-2(a), EMVI Negative (b) , CRM Negative (c), T1-3(d) , PCR(e) or Downstage after chemoradiotherapy(f) patients have a better OS.