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Original Article

Identifying high risk factors in locally advanced rectal cancer patients with ypT0-2N0 after preoperative chemoradiation

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Abstract: Objective: The objective of this study was to identify high risk factors for survival in locally advanced rectal cancer patients with ypT0-2N0 after neoadjuvant chemoradiation. Methods: In this study, Surveillance, Epidemiology, and End Results Program (SEER)-registered rectal cancer patients, and patients from Fudan University Shanghai Cancer Center (FUSCC) after preoperative chemoradiation were combined to identify poor prognostic patients with ypT0-2N0. Results: 2375 patients from SEER data and 106 patients from FUSCC were analyzed. The SEER data showed that less than 12 lymph nodes and mucinous/signet ring cancer were the two risk factors. The 5-year cancer specific survival (CSS) in patients with none, one or two risk factors was 91.5%, 88.5% and 70.3%, respectively ($P < 0.001$). Our cancer center data showed that less than 12 lymph nodes and mucinous/signet ring cancer were also the two risk factors. The 3-year disease free survival (DFS) in patients with none, one or two risk factors was 96.2%, 85% and 37.5%, respectively ($P = 0.013$). Conclusions: Two risk factors were identified in this study that correlated independently with a worse survival in patients with ypT0-2N0. The current results indicated that adjuvant chemotherapy may be not spared in these patients who have 1 or 2 risk factors.

Keywords: Rectal cancer, risk factors, good response, SEER

Introduction

Colorectal cancer is one of the most common cancers in the Western world and postoperative adjuvant chemotherapy with 5-fluorouracil (5-FU) based regimens is now the standard treatment in TNM stage III (and 'high-risk' stage II) colon cancer based on the results of large randomized clinical trials [1-5]. In contrast, clinical practice guideline of adjuvant chemotherapy of locally advanced rectal cancer is not based on solid evidence and the level of scientific evidence for sufficient benefit is much lower than colon cancer.

Two retrospective studies suggested that postoperative chemotherapy can be spared for patients whose tumors were downstaged to ypT0-2N0 after preoperative chemoradiation [6, 7]. However, about 10-15% of patients with ypT0-2N0 will develop recurrence.

Thus, we designed our study to identify poor prognostic ypT0-2N0 patients who may be not spared with adjuvant chemotherapy by analyzing the Surveillance, Epidemiology, and End Results (SEER)-registered database. Moreover, because SEER data lacks information on disease free survival (DFS), we further clarified the issue in another set of patients with locally advanced rectal cancer from the Fudan University Shanghai Cancer Center (FUSCC).

Materials and methods

Patient selection in the SEER database

The SEER, a population-based reporting system, was surveyed for the retrospective collection of data used in the analysis. The SEER program collects and publishes cancer incidence and survival data from 18 population-based cancer registries, covering > 25% of the US population. Because no personal identifying information was used in the analysis, this study was granted an exemption from the Institutional Review Board of the study institution on March 30, 2012.

Table 1. Patient characteristics from SEER database

Variable	n	%
Sex		
Male	1545	65.1
Female	830	34.9
Age		
< 50	418	17.6
≥ 50	1957	82.4
Race		
White	1956	82.4
Black	217	9.1
Other	202	8.5
Pathological grading		
Grade I	180	7.6
Grade II	1667	70.2
Grade III	195	8.2
Grade IV	10	0.4
Unknown	323	13.6
Histotype		
Adenocarcinoma	2299	96.8
Mucinous/Signet ring cell	76	3.2
No. of LNs dissected		
< 12	1482	62.4
≥ 12	893	37.6

Abbreviations: LNs, lymph nodes.

Cases of rectal cancer (C20.9 Rectum, NOS) from 2004 to 2011 were extracted from the SEER database (SEER*Stat 8.1.5) according to the Site Recode classifications with limitation to radiation prior to surgery and radiation preoperatively and post-surgery. Histological type were limited to adenocarcinoma (ICD-03, 8140/3, 8210/3, 8261/3, 8263/3), mucinous adenocarcinoma (ICD-03, 8480/3), and signet ring cell carcinoma (ICD-03, 8490/3). We selected this range because American Joint Committee on Cancer (AJCC) TMN stage was available since 2004 and chemoradiation has become the standard treatment since the landmark German CAO/ARO/AIO-94 trial using preoperative chemoradiation which was published in 2004. Other exclusion criteria were as follows: synchronous distance metastases, and patients with unknown TNM stage.

This study was based on the publicly available data from the SEER database and we had got the permission to access these research data (Reference number: 10963-Nov2014). It didn't include interaction with human subjects or use personal identifying information. The study did not require informed consent and was approved by the Review Board of Fudan University Shanghai Cancer Center, Shanghai, China.

Patient selection in the FUSCC

The Fudan University Shanghai Cancer Center Ethics Review Board approved the study. The written informed consent was not given by participants for their clinical records to be used in this study. Because patient records/information was anonymized and de-identified prior to analysis. Preoperative chemoradiation was performed as standard treatment of LARC since 2006, so we performed a retrospective consecutive cohort study of locally advanced rectal cancer patients with preoperative chemoradiation at FUSCC between 2006 and 2012. Patients were identified from our institutional patient colorectal cancer database. Patients with synchronous distance metastases, and unknown TNM stage were excluded.

Treatment details

Pretreatment clinical stage was assessed on the basis of MRI. All pretreatment biopsies were reviewed and diagnoses confirmed by Shanghai Cancer Center gastrointestinal pathologists. All patients also underwent full colonoscopic evaluation to exclude synchronous tumors, as well as digital rectal examination and proctoscopy to identify the tumor distance from the anal verge. Patients were treated with chemoradiotherapy with a median radiotherapy dose of 50 Gy and concurrent fluorouracil-based chemotherapy. Surgery generally was performed 6 to 8 weeks following completion of chemoradiotherapy and included low anterior resection, or abdominoperineal resection using total mesorectal excision (TME) principles. Standard pathologic tumor staging of the resected specimen was performed after resection in accordance with the guidelines of the College of American Pathologists, with histopathologic diagnosis performed by dedicated gastrointestinal cancer pathologists. The gross tumor volume was entirely embedded and serially sectioned for hematoxylin and eosin staining and microscopic evaluation. Postoperative follow-up consisted of routine physical examination with carcinoembryonic antigen measurement and cross-sectional imaging every 3-6 months for the first 2 years after completion of treatment and every 6-12 months

Table 2. Univariate survival analyses of patients according to various clinicopathological variables from SEER database

Variable	Log rank test	P
Sex	1.159	0.282
Male		
Female		
Age	4.573	0.032
< 50		
≥ 50		
Race	11.428	0.003
White		
Black		
Other		
Pathological grading	5.29	0.259
Grade I		
Grade II		
Grade III		
Grade IV		
Unknown		
Histotype	13.604	< 0.001
Adenocarcinoma		
Mucinous/Signet ring cell		
No. of LNs dissected	8.881	0.003
< 12		
≥ 12		

Abbreviations: LNs, lymph nodes.

Table 3. Multivariate Cox model analyses of prognostic factors of CSS

Variable	Hazard ratio		P
Sex			0.306
Male	1.000	Reference	
Female	0.850		
Age			0.061
< 50	1.000	Reference	
≥ 50	1.522		
Race			0.315
Other	1.000	Reference	
White	1.243		
Black	1.566		
Pathological grading			0.838
Grade I	1.000	Reference	
Grade II	1.143		
Grade III	1.366		
Grade IV	2.342		
Unknown	2.523		
Histotype			0.001
Adenocarcinoma	1.000	Reference	
Mucinous/Signet ring cell	2.612		
No. of LNs dissected			0.005
< 12	1.000	Reference	
≥ 12	0.619		

for 2 additional years thereafter. CT scans of the chest, abdomen and pelvis, full colonoscopic evaluation, and/or positron emission tomography (PET) were immediately performed if any symptom of disease occurred or elevated tumor marker levels were detected.

Statistical analysis

Age, sex, race, total number of LNs examined, histological grade, histotype and cancer specific survival (CSS) were extracted from SEER database. CSS was calculated from the date of diagnosis to the date of cancer specific death. Deaths attributed to the rectal cancer were treated as events and deaths from other causes were treated as censored observations.

Age, gender, yp stage, the form of surgery, baseline stage, distance from anal verge, No. of LNs dissected, pathologic type, disease free survival (DFS) were extracted from our cancer center database. The sites of relapse were classified as local recurrence and distant failure. Local recurrence was defined as recurrence within the pelvis, including the tumor bed, regional lymph nodes, anastomosis, or perineal scar. Distant failure was indicated as disease recurrence detected in the liver, lung, brain, and other organs outside the pelvis. For DFS analysis, patients for whom treatment had failed were identified at the time of disease recurrence or death from any cause. The Kaplan-Meier method was used to estimate the CSS and DFS [8]. The association between each of the potential prognostic factors and the estimated CSS and DFS was tested with the log-rank test [9]. Multivariate analysis was performed using the Cox regression model [10]. The statistical test was two sided and $P < 0.05$ was considered statistically significant. PASW Statistics 13 (SPSS Inc., Chicago, USA) was used for the statistical analysis.

Results

SEER database patient characteristics

A total of 2375 eligible patients during the 8-year study period were identified, including 1545 male and 830 female patients. Patient demographics and pathological features are summarized in **Table 1**.

Potential risk factors and prognostic significance

All potential risk factors, including sex, age, race, pathological grading, histotype and No. of

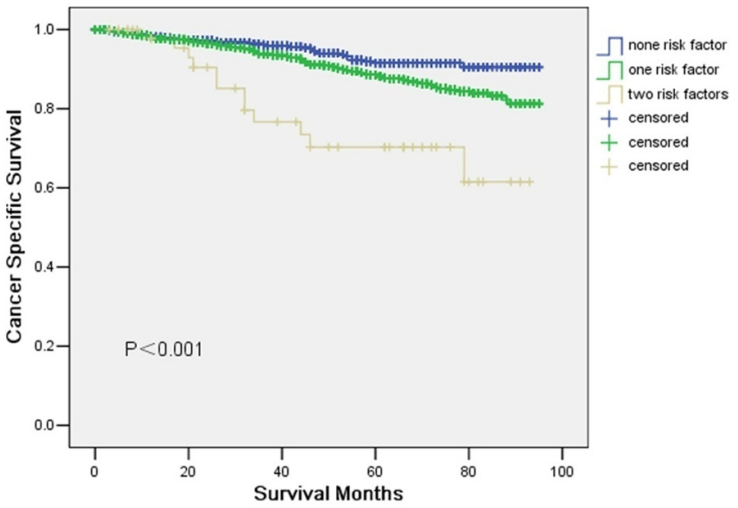

Figure 1. Cancer specific survival curves in rectal cancer patients according to number of risk factors. The 5-year cancer specific survival (CSS) in patients with none, one or two risk factors was 91.5%, 88.5% and 70.3%, respectively (P < 0.001).

Table 4. Demographic and clinical features of patients with rectal cancer from Fudan University Shanghai Cancer Center

Variable	n	%
Age (yr)		
< 50	39	36.8
≥ 50	67	63.2
Gender		
Male	71	67
Female	35	33
Pathologic type		
Adenocarcinoma	102	96.2
Mucinous/Signet ring cell	4	3.8
Baseline stage		
II	22	20.8
III	84	79.2
Distance from anal verge		
≤ 5 cm	70	66
> 5 cm	36	34
yp stage		
T0N0	45	42.5
T1-2N0	61	57.5
Surgery		
Low anterior resection	37	34.9
Abdominoperineal resection	69	65.1
Lymphovascular invasion	4	3.8
Perineural invasion	1	0.9
No. of LNs dissected		
< 12	54	50.9
≥ 12	52	49.1
Follow-up duration, months		
Median	38	
Range	19-98	

LNs dissected, were evaluated by using the Kaplan-Meier method (compared with Log rank test). Among six potential risk factors, age, race, histotype and No. of LNs dissected exhibited a correlation with CSS (**Table 2**). Cox multivariate regression analysis revealed only two factors to be associated with CSS: histotype and No. of LNs dissected (**Table 3**). The 5-year CSS in patients with none, one or two risk factors was 91.5%, 88.5% and 70.3%, respectively (P < 0.001) (**Figure 1**).

Evaluating the SEER database outcomes using the FUSCC set

The above results should be treated with caution as they lack information on DFS. To evaluate the reliability of SEER results, we studied relevant issues in 106 eligible patients from the FUSCC. Patient demographics and pathological features are summarized in **Table 4**.

Potential risk factors and prognostic significance

All potential risk factors, including age, gender, yp stage, the form of surgery, baseline stage, distance from anal verge, No. of LNs dissected and pathologic type were evaluated by using the Kaplan-Meier method (compared with Log rank test). Among these potential risk factors, age, No. of LNs dissected and pathologic type exhibited a correlation with DFS (**Table 5**). Cox multivariate regression analysis revealed only two factors to be associated with DFS: No. of LNs dissected and pathologic type (**Table 6**). The 3-year DFS in patients with none, one or two risk factors was 96.2%, 85% and 37.5%, respectively (P = 0.013) (**Figure 2**).

Discussion

Treatment response to neoadjuvant chemoradiotherapy is an early surrogate marker and correlated to oncologic outcomes in rectal cancer. Park *et al.* showed complete response of neoadjuvant chemoradiotherapy had excellent 5-year recurrence free survival of 90.5% [23]. In addition, Fietkau *et al.* indicated that 3-year disease free survival for patients with ypN0 was excellent, independent of whether

Table 5. Univariate survival analyses of patients according to various clinicopathological variables from FUSCC database

Variable	Log rank test	P
Age	4.258	0.039
< 50		
≥ 50		
Gender	0.13	0.718
Male		
Female		
yp stage	0.824	0.364
pCR		
yp I		
Surgery	0.374	0.541
Low anterior resection		
Abdominoperineal resection		
Distance from anal verge (cm)	0.075	0.785
≤ 5		
> 5		
Baseline stage	0.125	0.724
II		
III		
No. of LNs dissected	4.179	0.041
< 12		
≥ 12		
Pathologic type	6.177	0.013
Adenocarcinoma		
Mucinous/Signet ring cell		

they had received postoperative chemotherapy (87.5 ± 6.0 percent) or not (87.7 ± 6.7 percent) [7]. However, about 10-15% of locally advanced rectal cancer patients with good response of neoadjuvant treatment will develop recurrence and it is important to find risk factors associated with recurrence. In multivariate analyses, Fietkau *et al.* suggested that age, gender, kind of chemotherapy applied simultaneously to the irradiation, postoperative chemotherapy, type of surgery and tumor localization were not correlated with disease free survival. This would be consistent with our work. In our study, multivariate analysis revealed that less than 12 lymph nodes and mucinous/signet ring cancer were the two independent prognostic factors for CSS and DFS (P = 0.005 and P = 0.001, P = 0.035 and P = 0.021, respectively).

The current recommendation that a minimum of 12 lymph nodes should be examined to accurately stage colorectal cancers and this is mainly based on the rationale that an increase in the sampling would be associated with a decrease in the probability of understaging [11-13]. However, the association between neoadjuvant chemo-radiotherapy and a decreased number of LNs retrieved from TME specimen is widely accepted. In a recent publication from Marks *et al*., only 28% of 176 patients with rectal cancer undergoing neoadjuvant chemoradiation followed by TME proctectomy had greater that 12 LN Retrieved [14]. Govindarajan *et al.* from the Memorial Sloan-Kettering Cancer Center showing that among 429 rectal cancer patients undergoing neoadjuvant treatment and TME proctectomy, the mean number of LNs examined was 10 and 63% of the patients had less than 12 LNs identified in the surgical specimen [15].

Our study found that 37.6% of 2375 and 49% of 106 patients with ypT0-2N0 had greater than 12 LNs retrieved. The impact of LNs reduction after neoadjuvant chemoradiotherapy on oncologic outcomes has been the subject of constant discussion. Luna Perez *et al.* indicated that retrieval of at least 11 lymph nodes in the surgical specimen was not only a powerful tool to properly stage patients with rectal adenocarcinoma, but it was also of prognostic relevance in that 5-year survival and local recurrence were better in this group of patients [16]. In addition, Tsai *et al.* conducted a study on 372 patients with lymph node-negative rectal cancer who received preoperative chemoradiation; patients who had > 7 lymph nodes had higher 5-year rates of freedom from relapse (86% vs. 72%, P = 0.005) than those with ≤ 7 lymph nodes retrieved [17]. In contrast, a recent study from Kim *et al.* found that retrieval of ≥ 12 lymph nodes was an independent prognostic factor for disease-free survival among patients with a good tumor response (TRG 3-4) and those with < 12 lymph nodes retrieved had a significantly better 3-year DFS than those with ≥ 12 lymph nodes retrieved (P = 0.030) [18]. Four recent retrospective studies have failed to show any correlation between the number of lymph nodes retrieved and patient outcome after rectal cancer surgery after preoperative chemoradiation [19-22]. In the present study, less than 12 lymph nodes retrieval after preoperative chemoradiotherapy for rectal cancer is associated with lower 5-year CSS and 3-year

Table 6. Multivariate Cox model analyses of prognostic factors of DFS

Variable	Hazard ratio		P
Age			0.159
< 50	1.000	Reference	
≥ 50	0.314		
Gender			0.516
Male	1.000	Reference	
Female	1.552		
yp stage			0.426
pCR	1.000	Reference	
yp I	1.808		
Surgery			0.863
Low anterior resection	1.000	Reference	
Abdominoperineal resection	1.166		
Distance from anal verge (cm)			0.93
≤ 5	1.000	Reference	
> 5	0.925		
Baseline stage			0.976
II	1.000	Reference	
III	0.974		
No. of LNs dissected			0.035
< 12	1.000	Reference	
≥ 12	0.174		
Pathologic type			0.021
Adenocarcinoma	1.000	Reference	
Mucinous/Signet ring cell	13.855		

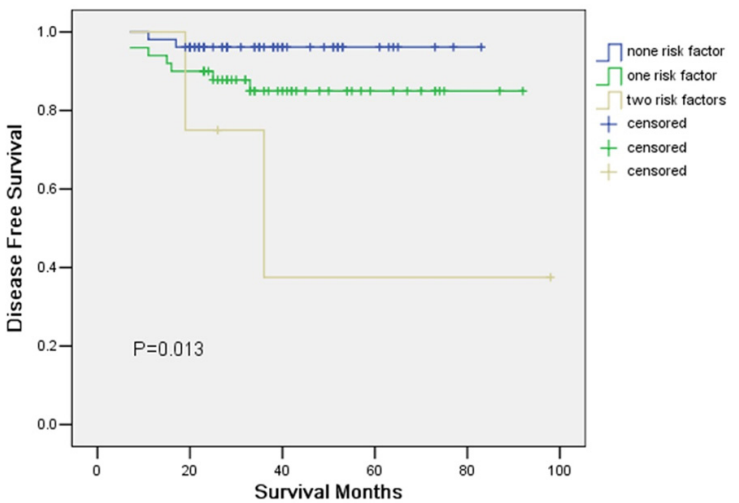

Figure 2. Disease free survival curves in rectal cancer patients according to number of risk factors. The 3-year disease free survival (DFS) in patients with none, one or two risk factors was 96.2%, 85% and 37.5%, respectively (P = 0.013).

disease-free survival (P = 0.003 and P = 0.041) in patients with ypT0-2N0.

Our study has several limitations that deserve mention. First, although the present study is a large population-based study, the SEER database does not include information regarding the administration of CRT and the quality of surgical care or pathological technique, and all of these factors may affect positive LNs harvest. Second, it is a retrospective analysis and was therefore limited by the bias inherent in this type of analysis. However, given that the study patients were consecutive, offering a non-selected series of ypT0-2N0 rectal cancers, we believe that our results do not reflect a bias toward patients.

In conclusion, less than 12 lymph nodes and mucinous/signet ring cancer were the two risk factors. The current results indicated that adjuvant chemotherapy may be not spared in these patients who have 1 or 2 risk factors.

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Disclosure of conflict of interest

None.

Authors' contribution

JFW and ZZ conceived of and designed the study. JFW, MHL, LFY and GCL performed the analyses. JZ and GCL prepared all tables. JFW and ZZ wrote the main manuscript. All authors reviewed the manuscript.

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