Iran J Public Health, Vol. 52, No. 9, Sep 2023, pp.1935-1941

Original Article

Response to Neoadjuvant Chemoradiotherapy as a Predictor of Long-Term Survival in Patients with Locally Advanced Rectosigmoid Junction Cancer: An Analysis Based On SEER Database

Qi Shen [1], Dandan Liu [2], *Shaojun Liu [3]

1. *Department of Radiation Oncology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui,230001, China*
2. *Department of Geriatric Medicine, The Second People's Hospital of Hefei (Hefei Hospital Affiliated to Anhui Medical University), Hefei, Anhui, 230001,China*
3. *Department of General Surgery, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, 230001,China*

***Corresponding Author:** Email: liusj0621@163.com

(Received 15 Feb 2023; accepted 06 Apr 2023)

Abstract

Background: Neoadjuvant chemoradiotherapy is recommended to locally advanced rectal cancer, especially for the lower and middle ones. However, the role of neoadjuvant chemoradiotherapy in rectosigmoid junction cancer remains undetermined. We investigated whether patients with a good response to neoadjuvant chemoradiotherapy will have a relatively better long-term survival compared with those with no response.

Methods: Overall, 1325 patients diagnosed with locally advanced rectosigmoid junction cancer from Surveillance, Epidemiology, and End-Results (SEER) cancer registry database (2004-2014, America) were selected. All of them had received neoadjuvant chemoradiotherapy and were evaluated by Collaborative Stage Data Collection System. We performed Kaplan–Meier univariate analysis and Cox regression multivariate analysis models to estimate the potential prognostic factors of long-term survival outcomes. Response to neoadjuvant chemoradiotherapy and histological type of tumor were the two prognostic factors.

Results: The 5-year OS was 78.1% in responders, and 63.4% in nonresponders. In addition the 5-year DSS was 85.1% in responders, and 72.9% in nonresponders.

Conclusion: Based on SEER database in locally advanced rectosigmoid junction cancer, patients with a good response to neoadjuvant chemoradiotherapy could have a benefit of long-term survival.

Keywords: Rectosigmoid junction cancer; Neoadjuvant therapy; Chemoradiotherapy; Long-term survival; Treatment outcome

Introduction

Colorectal cancer is one of the most common cancers and one of the most common causes of cancer death worldwide especially in developed countries (1). Neoadjuvant chemoradiotherapy is

proved beneficial to local control and survival in rectal cancer, although its survival benefit remains controversial when comparing with adjuvant chemoradiotherapy (2-5). It is widely accepted that neoadjuvant chemoradiotherapy is the current standard treatment for locally advanced rectal cancer, while there is no solid evidence to support the benefit for patients with colon cancer. Considering its location, rectosigmoid junction cancer maybe acts differently from rectal cancer and colon cancer. Anatomically rectosigmoid junction is a part of the distal colon and some researches shows that survival of patients with stage II/III rectosigmoid junction cancer is similar to colon cancer, therefore someone declare that rectosigmoid junction cancer should be classified as colon cancer (6). However, radiotherapy improves survival of patients with rectosigmoid junction cancer which is distinct from colon cancer and rectosigmoid junction shares crucial vascular system with the upper rectum above peritoneal reflection, hence others insist that rectosigmoid junction cancer is an independent tumor type rather than a type of colon cancer or rectal cancer (7, 8). Due to the inconclusive opinions of rectosigmoid junction cancer, it is meaningful to investigate the role of neoadjuvant chemoradiotherapy in rectosigmoid junction cancer.

SEER (Surveillance, Epidemiology, and End-Results) cancer registry database is an authoritative source of cancer-related information in the United States. It is sponsored by the National Cancer Institute (NCI). It provides population-based clinical data for various cancers. In currently running version of SEER database, according to Third Edition of International

Classification of Diseases for Oncology (ICD-O-3), rectosigmoid junction cancer is classified as an independent tumor site coded with C19.9. Based on SEER database, Rectosigmoid junction cancer patients received neoadjuvant or adjuvant radiotherapy had a better 5-year disease specific survival (DSS) and overall survival (OS) than surgery alone, however the benefit between neoadjuvant and adjuvant radiotherapy had no significant difference (7). Considering that neoadjuvant chemoradiotherapy presents obvious advantages in rectal cancer, especially in middle and lower ones, the role of neoadjuvant chemoradiotherapy in locally advanced rectosigmoid junction cancer is worthy of attention.

The aim of the study was to figure out prognostic factors of locally advanced rectosigmoid junction cancer among patients who received neoadjuvant chemoradiotherapy and surgery.

Materials and Methods

Patient selection

Information of patients diagnosed with locally advanced rectosigmoid junction cancer during 2004-2014 were collected from SEER database (SEER*Stat 8.3.4). AJCC 6th or 7th edition stage II and stage III were defined as locally advanced rectosigmoid junction cancer in this study. Then we selected the patients who received neoadjuvant chemoradiotherapy followed by surgical resection and had been evaluated the tumor size or extent by postoperative pathologic evidence. Their detailed clinical and pathological information was recorded in Collaborative Stage Data Collection System in SEER database. All of the selected patients had been recorded CS tumor size/ext eval code "5" or "6". A total of 1325 patients were identified finally from SEER database.

Statistical analysis

The Kaplan–Meier univariate analysis was applied to generate overall survival curve and disease specific survival curve. The data difference of different responses to neoadjuvant chemoradiotherapy were analyzed by log-rank test. Sex, AJCC Stage, histological type, grade, age, CEA, regional lymph nodes, tumor deposits information were also extracted from SEER database to analyze the influence on survival. 5-year OS was calculated for different groups including for different responses to neoadjuvant chemoradiotherapy. Then we choose the clinical or pathological characteristics which P value <0.2 in univariate analysis to perform further multivariate analy-

sis. Cox regression model was applied in multivariate analysis. $P < 0.05$ was considered statistically significant. SPSS 19.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis.

Results

Patient characteristics

A total of 1,325 patients were finally selected from SEER cancer registry database (2004-2014, America), including 810 male (61.1%) and 515 female (38.9%) patients. There were 748 patients (56.5%) with AJCC III stage, 577 patients (43.5%) with AJCC II stage rectosigmoid junction cancer. According to the rules of Collaborative Stage Data Set, CS tumor size/ext eval code "5" was chosen only in circumstance that "surgical resection performed after neoadjuvant therapy and tumor size/extension based on clinical evidence, unless the pathologic evidence at surgery (after neoadjuvant) is more extensive" while code "6" was chosen only in circumstance that "surgical resection performed after neoadjuvant therapy and tumor size/extension based on pathologic evidence, because pathologic evidence at surgery is more extensive than clinical evidence before treatment". In another word, CS tumor size/ext eval code "5" represented for shrunken or stable tumor size or extent after neoadjuvant chemoradiotherapy, and code "6" represented for more extensive tumor size or extent. Therefore in this study we looked upon code "5" as responders to neoadjuvant chemoradiotherapy and code "6" as nonresponders.

All patient clinical and pathological characteristics are summarized in Table 1.

Table 1: Patient demographics and pathological characteristics

Characteristics	***Neoadjuvant chemoradiotherapy***		
	Responders (n=785) N(%)	Nonresponders (n=540) N(%)	All patients (n=1325)
Sex			
Male	479 (59.1)	331 (40.9)	810
Female	306 (59.4)	209(40.6)	515
AJCC Stage			
Stage II	332 (57.5)	245(42.5)	577
Stage III	453 (60.6)	295 (39.4)	748
Histologic Type			
Adenocarcinoma	650 (82.7)	446 (17.3)	1096
others	135 (59.0)	94 (41.0)	229
Grade			
Grade I	40 (54.1)	34 (45.9)	74
Grade II	563 (58.7)	96 (41.3)	959
Grade III	84 (53.5)	73 (46.5)	157
Grade IV	11 (68.8)	5 (31.2)	16
Unknown	87 (73.1)	32 (26.9)	119
Age			
<55 years	275 (59.7)	186 (40.3)	461
>=55 years	510 (59.0)	354 (41.0)	864
CEA			
Positive	253 (57.1)	190 (42.9)	443
Negative	296 (67.4)	143 (32.6)	439
Borderline	1 (14.3)	6 (85.7)	7
Unknown	235 (53.9)	201 (46.1)	436
Regional Lymph Nodes			
None	271 (55.2)	220 (44.8)	491
Positive	319 (69.3)	141 (30.7)	460
Unknown	195 (52.1)	179(47.9)	374
Tumor Deposits			
Positive	41 (41.8)	57 (58.2)	98
Negative	401(66.6)	201(33.4)	602
Unknown	343(54.9)	282 (45.1)	625

We extracted sex, AJCC stage, histologic type, grade, age, CEA, regional lymph nodes, tumor deposits information from SEER database to analyze. It was obviously that adenocarcinoma accounted for largest proportion of histological type, and grade II accounted for largest proportion of tumor grade. Furthermore stage III, adenocarcinoma, grade IV, CEA negative, regional lymph nodes positive, tumor deposits negative were in the majority of responders to neoadjuvant chemoradiotherapy.

Different responses to neoadjuvant chemoradiotherapy as a predictor of long-term survival outcomes in rectosigmoid junction cancer

There was significant difference in univariate log-rank test ($P < 0.001$) on overall survival (OS) and disease specific survival (DSS) of patients with rectosigmoid junction cancer between responders and nonresponders of neoadjuvant chemoradiotherapy (Fig. 1A and 1B). The 5-year OS was 78.1% in responders, and 63.4% in nonresponders. In addition the 5-year DSS was 85.1% in responders, and 72.9% in nonresponders. Besides, in patients with rectosigmoid junction cancer, histologic type, age, CEA, response to neoadjuvant chemoradiotherapy were factors affected OS on univariate analysis (Table 2). Patients of adenocarcinoma, younger than 55 years, CEA negative, responders of neoadjuvant chemoradiotherapy were considered to have better long-term survival. In the aim to investigate how the long-term survival was affected when considering all clinical factors together, multivariable proportional Cox model was constructed. Only response to neoadjuvant chemoradiotherapy and histological type of tumor were the two independent prognostic factors (Table 2). That is to say, it is authentic to look response to neoadjuvant chemoradiotherapy upon as an early long-term survival indicator for patients with locally advanced rectosigmoid junction cancer.

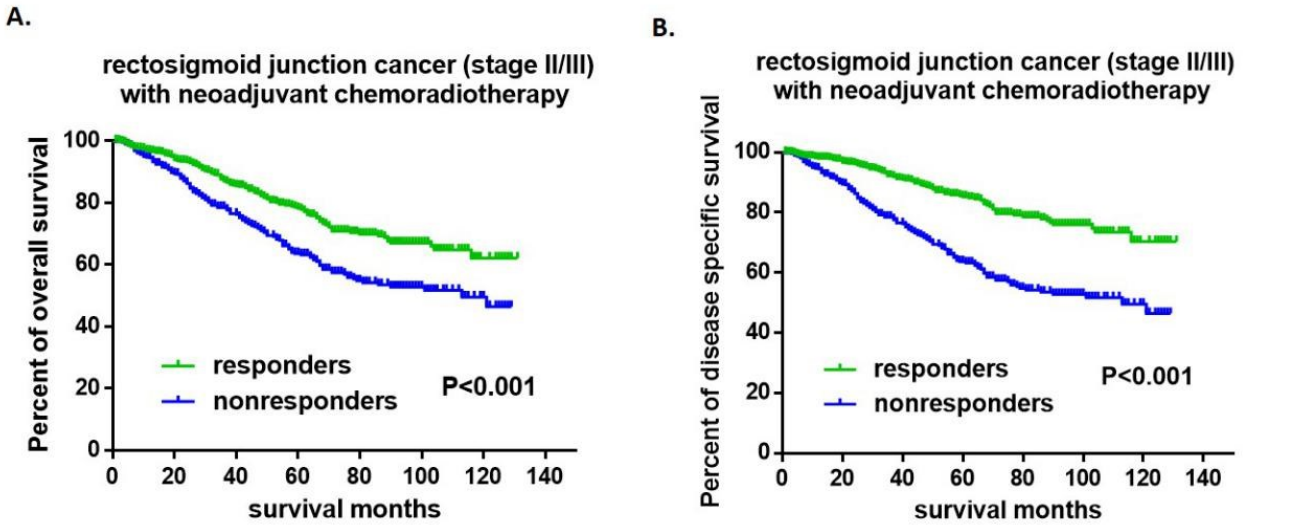

Fig. 1: Survival curve was generated by Kaplan-Meier univariate log-rank test ($P<0.001$) on overall survival (OS)(Fig. 1A) and disease specific survival (DSS) (Fig.1B) of patients with rectosigmoid junction cancer between responders and nonresponders of neoadjuvant chemoradiotherapy

Table 2: Univariate and multivariate analyses for patients with rectosigmoid junction cancer received neoadjuvant chemoradiotherapy

Characteristics	***5-year OS (%)***	***Univariate analysis*** *P value*	***Multivariate analysis*** *P value*
Sex		0.546	/
Male	71.0		
Female	72.5		
AJCC Stage		0.621	/
Stage II	80.9		
Stage III	78.7		
Histologic Type		<0.001	0.001
Adenocarcinoma	74.3		
others	58.1		
Grade		0.917	/
Grade I	82.4		
Grade II	71.4		
Grade III	74.0		
Grade IV	0.0		
Age		0.077	0.135
<55 years	75.7		
>=55 years	69.4		
CEA		<0.001	0.070
Positive	62.8		
Negative	76.7		
Borderline	55.6		
Regional Lymph Nodes		0.349	/
None	68.4		
Positive	73.7		
Tumor Deposits		0.517	/
Positive	71.2		
Negative	70.1		
Response to Neoadjuvant Chemoradiotherapy		<0.001	<0.001
Responders	78.1		
Nonresponders	63.4		

Discussion

As for rectosigmoid junction cancer, it is regarded as an independent type of colorectal cancer nowadays, but its optimum therapeutic strategy is still unfathomed. Rectosigmoid junction cancer locates between rectum and colon, its behavior maybe acts differently from either of them. Radiotherapy improves both survival and local control of rectal cancer. Neoadjuvant chemoradiotherapy is a current standard therapy of locally advanced rectal cancer. Comparing with adjuvant radiotherapy, better local control was seen in patients received neoadjuvant chemoradiotherapy, while benefit in long-term survival was controversial (2-5). When taking accurate tumor location into consideration, some researchers insisted that addition of radiotherapy in patients with locally advanced upper rectum cancer who have underwent total mesorectal excision (TME) has little benefit compared with TME only (9). When it came to rectosigmoid junction cancer, a previous SEER-based study showed that radiotherapy brought out better survival than surgery only, but

neoadjuvant radiotherapy gave no survival benefit compared with adjuvant radiotherapy (7). Besides, there was no other large population-based study was reported concerning neoadjuvant radiotherapy and long-term survival of patients with rectosigmoid junction cancer. In order to investigate into the role of neoadjuvant radiotherapy in locally advanced rectosigmoid junction cancer, we performed this analysis based on SEER database.
In rectal cancer, concurrent fluorouracil-based chemotherapy with neoadjuvant radiotherapy is the recommended therapy (10, 11). The optimal chemotherapy regimen is being studying. Combination with oxaliplatin to modified fluorouracil-based concurrent chemotherapy is feasible and effective to induce better local tumor response (11, 12). These studies tend to draw attention to the importance of concurrent chemotherapy in neoadjuvant therapy in rectal cancer. Therefore, to imitate the pattern of neoadjuvant therapy in rectal cancer, we select patients with rectosigmoid junction cancer who have received not only neoadjuvant radiotherapy but also chemotherapy in SEER database. Limited by not enough comprehensive information extracted from SEER database, such as the dose and fraction of neoadjuvant radiotherapy are not accessible in our study. Furthermore, recurrence data are also absent in SEER database, which restrict us from analyzing recurrence situation after the full course of neoadjuvant chemoradiotherapy and surgery. Survival analysis was performed comparing neoadjuvant chemoradiotherapy with adjuvant chemoradiotherapy in locally advanced rectosigmoid junction cancer, but no significant difference was found (data not shown). These results coincides with above-mentioned chemoradiotherapy researches in rectal cancer. Addition of chemotherapy did not improve the survival outcomes of patients who received neoadjuvant radiotherapy with locally advanced rectosigmoid junction cancer (7).
According to the rule of SEER database, we gave a definition of responders and nonresponders of neoadjuvant chemoradiotherapy. Comparing pathologic evidence at surgery after neoadjuvant therapy with clinical evidence before treatment, response to neoadjuvant chemoradiotherapy was evaluated. Because of the limitation of information recorded in SEER database, this evaluation is not so precise as widely accepted RECIST (Response Evaluation Criteria In Solid Tumors) which is a set of published rules that define when cancer patients improve, stay the same or worsen during treatments (13). Despite its imperfection, it helped us briefly evaluating the effect of neoadjuvant chemoradiotherapy. In the present study, long-term survival benefit was found in the responders of neoadjuvant chemoradiotherapy and in adenocarcinoma subgroups. Considering that in fact adenocarcinoma obviously takes the largest proportion of histologic types in the study (1096 in 1325 , 82.7%), predication of long-term survival on the basis of response to neoadjuvant chemoradiotherapy seems to have a more realistic meaning than the histologic prognostic factor. A variety of clinical studies in rectal cancer suggested that a good response to neoadjuvant radiotherapy +/- chemo associated with good long-term survival outcome (14, 15). Our study in locally advanced rectosigmoid junction cancer indicated similar circumstances to rectal cancer.

Conclusion

Response to neoadjuvant chemoradiotherapy and histological type of tumor are the two independent prognostic factors in locally advanced rectosigmoid junction cancer with neoadjuvant chemoradiotherapy. Evaluation of response to neoadjuvant chemoradiotherapy based on pathologic evidence at surgery and clinical evidence before treatment is considered necessary to carry out, owing to its certain meaning in prediction of survival outcome. Short-term good response to neoadjuvant chemoradiotherapy tends to be good for long-term survival in locally advanced rectosigmoid junction cancer.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission,

redundancy, etc.) have been completely observed by the authors.

Acknowledgements

The authors acknowledge Dr. Hongyan Zhang and Wenguang Luo for critical reading of the manuscript and helpful discussions.

Conflict of Interest

The authors declare that there is no conflict of interest.

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