Rectal NETs and rectosigmoid junction NETs may need to be treated differently

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INTRODUCTION

Neuroendocrine tumors (NETs) are heterogeneous tumors with malignant potential.1,2 The incidence has been rising, and a growing number of patients are diagnosed due to better diagnostic techniques.3,4 The projected prevalence of NETs in the US population in 2014 was 171,321.5

The rectum is among the most common locations of digestive NETs (approximately 1.2/100,000 population),6 and the relative incidence of rectal NETs may be higher in Asian populations.1,2
countries (approximately 50% of digestive NETs). If the
disease is treated during the early stage, rectal NETs are as-
symptomatic and indolent, and the 5-year survival rate is high
(62%-88%). However, survival is markedly worse when the
disease is reginal or distant (24%-33%).

Many different definitions have been used to divide the
rectum, and its length remains controversial. Commonly, in
clinical practice, we use the American Joint Committee on
Cancer (AJCC) staging system, which proposes 16 cm as the
upper limit of the rectum, and rectosigmoid junction tumors
are defined as tumors between the sigmoid and rectum.

According to the AJCC staging system, the rectosigmoid
junction is a part of the rectum close to the colon, and as is
well known, the overall survival of colonic NET patients is
significantly worse than that of rectal NETs patients, which
provoked our curiosity regarding the survival of patients with
NETs located in the rectosigmoid junction. Additionally, we
observed that several rectosigmoid junction NET patients
shared a better survival in clinical practice, which was con-
trary to our thinking. The National Comprehensive Cancer
Network guidelines recommend radical resection with lymph
node dissection for rectal NETs >2 cm in diameter, and
many studies have confirmed that the tumor size is a vital
factor in predicting lymph node metastasis, which is im-
portant for deciding whether endoscopic therapies should
be performed. If patients with NETs in the rectosigmoid
junction and rectum exhibit significantly different survival
rates, the risk factors may also differ.

Therefore, we included patients from the Surveillance,
Epidemiology, and End Results Program (SEER) database,
which defined rectosigmoid junction and rectum NETs ac-

2 MATERIALS AND METHODS

2.1 Data collection and patient selection

The data were retrieved from the Surveillance, Epidemiology,
and End Results (SEER) database based on the November
2018 submission of patients diagnosed with NETs located
in the rectosigmoid junction and rectum between 2000 and
2016. We used the SEER*Stat 8.3.5 program to identify in-
dividuals in the SEER database as follows: ICD-O-3:8240
and 8249, and primary site codes: C19.9 rectum and C20.0
rectosigmoid junction. We excluded patients who met the
following criteria: (a) patients whose survival data or follow
up data were incomplete; (b) patients diagnosed with more
than one primary tumor; and (c) patients whose death was
due to nonneoplastic disease. Because many patients were
still in the active follow up stage and the overall survival
has not been achieved, we set the 5-year survival as the end
point. A flow diagram of the selection process is presented in
Figure 1.

2.2 Definition of data

Only NETs were included in our research. The definition of
rectosigmoid in the SEER database and the AJCC 8th staging
system is as follows: the rectosigmoid colon joins the sig-
moid colon to the rectum. The rectosigmoid is also known
as the upper rectum and is generally above the peritoneal
reflection. The description of the SEER staging system is
as follows: localized stage (entirely confined to the organ of
origin), regional stage (extending beyond the organ of origin
and/or regional nodal spread), and distant stage (distant me-
tastasis or extension).

2.3 Statistical analysis

The mean values are used to describe the continuous data,
and the discrete variables are displayed as the totals and fre-
quencies. The patients’ demographic data and tumor char-
acteristics are summarized using descriptive statistics. The
comparisons of the categorical variables among the different
groups of patients were performed using the chi-square test.
The survival function estimates and comparisons among the
different variables were performed using the Kaplan-Meier
method and the log-rank test. A Cox proportional hazards
model was used to compare the effects of the prognostic vari-
able on survival. A univariate analysis was performed using
the $\chi^2$ test or Student $t$ test. Then, a multivariable logistic re-
gression was performed to assess the associations among the
demographic/clinical factors, surgical procedure performed,
and the presence of lymph node metastasis at the time of
diagnosis.

All statistical analyses were performed using Intercooled
Stata 12.0 (Stata Corporation). The results were considered
statistically significant at a two-sided $P < .05$.

3 RESULTS

3.1 Basic characteristics of the patients

In total, 6675 patients with rectal NETs and 329 patients with
rectosigmoid junction NETs, were eligible for the analysis. The
median age at diagnosis was similar (54.18-year-old in the rec-
tum patients and 54.66 year-old in the rectosigmoid junction
patients). There were no significant differences in the demo-
graphic information of the patients with NETs in the two loca-
tions (sex, race, and rate of primary site surgery, all $P > .05$).
Significant differences could be found in the tumor characteristics, including differentiation, the SEER stage, the TNM stage, and the tumor size, between the patients with NETs in the two locations, and these differences are summarized in Table 1. The NETs in the rectum had a smaller tumor size and were more likely to be diagnosed in the early stage than the NETs in the
rectosigmoid junction. We performed multivariate analysis of including patients to identify factors affecting patients’ prognosis and presented it in Table 2. The results suggested that the location of primary site (HR = 0.82, 95% CI 0.70-0.95; P = .01) and TNM stage IV (HR = 2.40, 95% CI 1.30-4.21; P = .01) will affect patients’ prognosis. Therefore, we further investigated the

**Table 1** Demographic and clinical characteristics of patients

|                        | Rectum (%) | Rectosigmoid Junction (%) | P-value |
|------------------------|------------|---------------------------|---------|
| Median age of diagnosis| 54.18      | 54.66                     | .70     |
| Gender                 |            |                           | .27     |
| Male                   | 3273 (49.03)| 151 (45.90)              |         |
| Race                   |            |                           | .13     |
| White                  | 3584 (53.69)| 184 (55.93)              |         |
| Black                  | 1555 (23.30)| 83 (25.23)               |         |
| Other                  | 1536 (23.01)| 62 (18.84)               |         |
| Differentiation        |            |                           | .02     |
| Well                   | 2581 (38.67)| 100 (30.40)              |         |
| Moderately             | 423 (6.34) | 21 (6.38)                |         |
| Poor                   | 21 (0.31)  | 2 (0.61)                 |         |
| Unreport               | 3650 (54.68)| 206 (62.61)              |         |
| SEER stage             |            |                           | <.01    |
| Localized              | 6491 (97.24)| 304 (92.40)              |         |
| Regional               | 68 (1.02)  | 14 (4.26)                |         |
| Distant                | 116 (1.74) | 11 (3.34)                |         |
| T stage                |            |                           | <.01    |
| T1                     | 3932 (58.91)| 174 (52.89)              |         |
| T2                     | 131 (1.96) | 8 (2.43)                 |         |
| T3                     | 47 (0.7)   | 8 (2.43)                 |         |
| T4                     | 12 (0.18)  | 2 (0.61)                 |         |
| Unreport               | 2553 (38.25)| 137 (41.64)              |         |
| N stage                |            |                           | <.01    |
| N0                     | 6601 (98.89)| 310 (94.22)              |         |
| N1                     | 74 (1.11)  | 19 (5.78)                |         |
| M stage                |            |                           | .03     |
| M0                     | 6559 (98.26)| 318 (96.66)              |         |
| M1                     | 116 (1.74) | 11 (3.34)                |         |
| Tumor size             |            |                           | <.01    |
| <1 cm                  | 3932 (58.91)| 174 (52.89)              |         |
| 1-1.5 cm               | 131 (1.96) | 8 (2.43)                 |         |
| 1.5-2 cm               | 47 (0.70)  | 8 (2.43)                 |         |
| >2 cm                  | 12 (0.18)  | 2 (0.61)                 |         |
| Unreport               | 2553 (38.25)| 137 (41.64)              |         |
| Primary site surgery   |            |                           | .07     |
| Yes                    | 5884 (88.15)| 279 (84.80)              |         |
| No                     | 791 (11.85)| 50 (15.20)               |         |

**Table 2** Identify clinical factors association with prognosis using multivariate analysis

|                        | HR (95% CI) | P-value |
|------------------------|-------------|---------|
| Age of diagnosis       | 1.00 (0.99-1.00) | .75     |
| Gender                 |             |         |
| Female                 | Reference   | Reference|
| Male                   | 1.01 (0.95-1.08) | .80     |
| Race                   |             |         |
| White                  | Reference   | Reference|
| Black                  | 1.03 (0.95-1.11) | .46     |
| Other                  | 1.05 (0.96-1.14) | .32     |
| Location               |             |         |
| Rectum                 | Reference   | Reference|
| Rectosigmoid Junction  | 0.81 (0.69-0.94) | .01     |
| Differentiation        |             |         |
| Well                   | Reference   | Reference|
| Moderately             | 0.91 (0.81-1.03) | .14     |
| Poor                   | 1.01 (0.63-1.63) | .96     |
| TNM stage              |             |         |
| I                      | Reference   | Reference|
| II                     | 1.03 (0.81-1.30) | .80     |
| III                    | 1.37 (0.97-1.95) | .12     |
| IV                     | 2.40 (1.30-4.21) | .01     |
| Tumor size             |             |         |
| <1 cm                  | Reference   | Reference|
| 1-1.5 cm               | 1.00 (0.86-1.17) | .96     |
| 1.5-2 cm               | 1.16 (0.89-1.50) | .27     |
| >2 cm                  | 1.06 (0.91-1.22) | .45     |

relationship among tumor location, regional or distant metastasis and patients’ survival in the following.

### 3.2 Survival analysis and risk factors

We set the 5-year survival as the endpoint to perform further survival analysis because many patients were still in the follow up stage. In total, 6405 rectal NETs and 317 rectosigmoid junction NET patients were included in the analysis.

We found that the patients with NETs in the rectosigmoid junction had a significantly better survival than those with rectal NETs (HR = 0.82, 95% CI 0.70-0.95; P = .01) as shown in Figure 1 (P = .01, log-rank test). We further performed a multivariate analysis of the two different locations, and the factors affecting survival differed. In the rectum, the risk factors were the same as those reported in many previous studies18,19; poorer tumor differentiation (HR = 0.89, 95% CI 0.88-0.90; P < .01; poor differentiation as the reference), deeper invasion (HR = 1.47, 95% CI
1.11-1.95; \( P < .01 \); T1-T2 as the reference), lymph node metastasis (HR = 1.29, 95% CI 1.01-1.66; \( P = .04 \); N0 as the reference), and distant metastasis (HR = 11.72, 95% CI 1.41-21.0; \( P < .01 \); M0 as the reference) increase the risk of tumor-related death. The risk factors among the patients with rectosigmoid junction NETs differed such that males had a better survival than the females (HR = 0.69, 95% CI 0.55-0.88; \( P < .01 \)). Poor tumor differentiation (HR = 0.88, 95% CI 0.86-0.91; \( P < .01 \); poor differentiation as the reference), deeper invasion (HR = 2.97, 95% CI 1.30-6.77; \( P < .01 \); T1-T2 as the reference) and distant metastasis (HR = 6.09, 95% CI 2.74-13.56; \( P < .01 \); M0 as the reference) were still the main risk factors in rectosigmoid junction NETs (Figure 2). Primary surgery site could provide extra benefits to rectal NET patients (HR = 0.89, 95% CI 0.82-0.96; \( P < .01 \)), but the benefit was not significant in the rectosigmoid junction NET patients (HR = 0.91, 95% CI 0.65-1.26; \( P = .56 \)). We present these results in Table 3.

### 3.3 Different factors contribute to regional lymph node and distant metastases

Metastases definitely lead to worse survival. Therefore, we further analyzed the factors affecting regional lymph-node and distant metastases in the patients with tumors in the two locations, and the results are summarized in Tables 4 and 5.

After adjusting for age, sex, and race, we found that a T stage deeper than T1 and a tumor size larger than 1 cm could significantly increase the risk of regional lymph-node metastases in patients with rectal NETs (all OR > 5.00; \( P < .01 \)), which is consistent with many previous studies. In the rectosigmoid junction NET patients, a T stage deeper than T1 could definitely increase the regional lymph-node metastases risk (all OR > 5.00; \( P < .01 \)). Furthermore, a tumor size larger than 2 cm could significantly increase the regional lymph-node metastases risk (OR = 31.32, 95% CI 3.53-387.57; \( P < .01 \)), which differs from the patients with rectal NETs.

The risk factors of distant metastases slightly differed between patients with rectal NETs and rectosigmoid junction NETs. Patients older than 54 years (rectal NETs: OR = 1.03, 95% CI 1.01-1.04; \( P < .01 \); rectosigmoid junction NETs: OR = 1.11, 95% CI 1.03-1.21; \( P = .01 \)), male patients (rectal NETs: OR = 2.03, 95% CI 1.33-3.11; \( P < .01 \); rectosigmoid junction NETs: OR = 7.83, 95% CI 1.16-52.98; \( P = .04 \)) and regional lymph node metastases (rectal NETs: OR = 7.75, 95% CI 3.65-16.47; \( P < .01 \); rectosigmoid junction NETs: OR = 10.57, 95% CI 1.03-107.97; \( P < .01 \)) had a higher risk of distant metastases in both locations. In rectal NETs, an invasion deeper than T2 was associated with a high risk of distant metastases (OR = 95.85, 95% CI 44.87-204.73; \( P < .01 \)).

### 4 DISCUSSION

In this study, we reported an unexpected result that the 5-year survival significantly differed between patients with rectal NETs and those with rectosigmoid junction NETs. The patients with NETs in the rectosigmoid junction had a better survival than those with rectal NETs (HR = 0.82, 95% CI 0.70-0.95; \( P = .01 \)). We further explored the difference between the patients with rectal NETs and rectosigmoid junction NETs in many aspects. To the best of our knowledge, this study is the first to describe the difference between rectal NETs and rectosigmoid junction NETs.

At baseline, our study showed that the demographic information and surgery rate of the patients with NETs in the two locations were similar (all \( P > .05 \)), but the
characteristics of the tumors significantly differed, implying heterogeneity in the two locations. We also performed multivariate analysis of including patients which identified tumor locations and metastasis were factors affecting patients' prognosis. These results were the important basis of further analysis.

The rectosigmoid junction has been recognized as a distinct segment of the colon by the International Classification of Diseases for further heterogeneity in management and outcomes. The AJCC staging system and SEER database also separated the rectosigmoid junction, but to date, most of these tumors are treated as rectal tumors. In our study, the heterogeneities in rectosigmoid junction NETs were obvious, and we propose that future studies divide these NETs in data analyses. However, there are some opportunities and challenges. A standardized definition for the demarcation of the rectosigmoid junction is essential for further studies. However, a consensus has not been reached, which could increase the difficulties and bias in analyzing data from different countries or different data bases.

The German guidelines, TNM staging and SEER staging propose 16 cm as the upper limit of the rectum, whereas 15 cm has been proposed by the United States (ASCRS), United Kingdom and European guidelines (ESMO) and the UICC Manual. Other guidelines include a distance of 12 cm (Spanish guidelines) and 9 cm (Korea). Many studies have attempted to develop a definition because the therapeutic choice highly differs between colon and rectal adenocarcinoma. If a rectal tumor is misclassified as a sigmoid tumor, the patient could be inadequately staged and not considered for preoperative downstaging (chemo) radiation, potentially decreasing their chance of undergoing a complete resection and worsening their survival.

The factors affecting overall survival in patients with rectal NETs and rectosigmoid junction NETs also differed. In addition to the common factors, such as tumor differentiation, T stage and M stage, males had a better survival than females (HR = 0.69, 95% CI 0.55-0.88; \( P < .01 \)), and the benefits of primary surgery were not significant (HR = 0.91, 95% CI 0.65-1.26; \( P = .56 \)) in rectosigmoid junction NETs. As is well known, surgery is not the only way to remove tumors in the rectum. The optimal ways for primary resection in rectal NETs still remain controversial. Endoscopic resection has been shown to be effective in removing rectal NETs, particularly those measuring <10 mm in size. However, the treatment choices still vary because sufficient and convicive data are lacking, rendering it difficult to ensure complete

| TABLE 3 Multivariate analyses of overall survival of including patients |
|---------------------------------------------------------------|
| **Rectum**                                                     | **Rectosigmoid Junction** |
| **Multivariate analyses**                                     | **Multivariate analyses** |
| Age of diagnosis                                              | Age of diagnosis          |
| HR (95% CI)                                                   | HR (95% CI)               |
| P-value                                                       | P-value                   |
| 1.00 (0.99-1.01)                                              | 1.00 (0.99-1.01)          |
| .73                                                           | .45                       |
| Gender                                                        | Gender                    |
| Female Reference                                              | Female Reference          |
| Male 1.03 (0.98-1.08)                                         | Male 0.69 (0.55-0.88)     |
| .27                                                           | <.01                      |
| Race 0.99 (0.98-1.01)                                         | Race 1.04 (0.98-1.03)     |
| .62                                                           | .17                       |
| Differentiation 0.89 (0.88-0.90)                              | Differentiation 0.88 (0.86-0.91) |
| <.01                                                          | <.01                      |
| Tumor size 1.01 (1.00-1.01)                                   | Tumor size 1.00 (0.97-1.03) |
| .06                                                           | .84                       |
| T stage                                                       | T stage                   |
| T1-T2 Reference                                              | T1-T2 Reference           |
| 1.47 (1.11-1.95)                                              | 2.97 (1.30-6.77)          |
| <.01                                                          | <.01                      |
| T3-T4 1.67 (1.58-1.76)                                        | T3-T4 1.73 (1.36-2.19)    |
| <.01                                                          | <.01                      |
| N stage                                                       | N stage                   |
| N0 Reference                                                  | N0 Reference              |
| 1.29 (1.01-1.66)                                              | 1.14 (0.60-2.16)          |
| .04                                                           | .68                       |
| M stage                                                       | M stage                   |
| M0 Reference                                                  | M0 Reference              |
| 11.72 (1.41-2.10)                                             | 6.09 (2.74-13.56)         |
| <.01                                                          | <.01                      |
| Primary site surgery                                          | Primary site surgery      |
| No Reference                                                  | No Reference              |
| 0.89 (0.82-0.96)                                              | 0.91 (0.65-1.26)          |
| <.01                                                          | .56                       |
tumor resection and lower the rate of recurrence. The North American Neuroendocrine Tumors Society guidelines conclude that tumors <2 cm that are confined to the mucosa or submucosa are associated with very minimal risk of local and metastatic spread, and metastatic screening or follow-up are not recommended after local resection. In contrast, the National Comprehensive Cancer Network guidelines suggest that all patients should be screened with colonoscopy plus either abdominal/pelvic CT/MRI and endorectal ultrasound or endoscopic ultrasound. In addition, for lesions ≤2 cm, the

### Table 4

Predictors of regional lymph nodes metastases

|                | Rectum Multivariate analyses | Rectosigmoid Junction Multivariate analyses |
|----------------|------------------------------|--------------------------------------------|
|                | OR (95% CI)                  | P-value                                   |
| Age of diagnosis | 0.99 (0.98-1.01)             | .41                                        |
| Gender          | 1.12 (0.67-1.87)             | .66                                        |
| Race            | 0.95 (0.79-1.12)             | .49                                        |
| Differentiation | 0.98 (0.91-1.04)             | .46                                        |
| T stage         |                              |                                            |
| T1              | Reference                    | Reference                                 |
| T2              | 7.31 (2.97-17.99)            | <.01                                       |
| T3              | 47.80 (20.30-112.60)         | <.01                                       |
| T4              | 37.22 (9.00-153.89)          | <.01                                       |
| Unreport        | 2.41 (1.26-4.61)             | <.01                                       |
| Tumor size      |                              |                                            |
| <1 cm           | Reference                    | Reference                                 |
| 1-1.5 cm        | 20.10 (5.36-75.38)           | <.01                                       |
| 1.5-2 cm        | 66.72 (17.50-254.36)         | <.01                                       |
| >2 cm           | 25.40 (7.16-90.05)           | <.01                                       |
| Unreport        | 5.62 (1.66-19.08)            | <.01                                       |

### Table 5

Predictors of distant metastases

|                | Rectum Multivariate analyses | Rectosigmoid Junction Multivariate analyses |
|----------------|------------------------------|--------------------------------------------|
|                | OR (95% CI)                  | P-value                                   |
| Age of diagnosis |                              |                                            |
| <54-year-old   | Reference                    | Reference                                 |
| >54-year-old   | 1.03 (1.01-1.04)             | .01                                        |
| Gender         |                              |                                            |
| Female         | Reference                    | Reference                                 |
| Male           | 2.03 (1.33-3.11)             | <.01                                       |
| Race           | 0.88 (0.76-1.02)             | .10                                        |
| Differentiation| 1.05 (0.99-1.07)             | .07                                        |
| Tumor size     | 1.01 (0.95-1.69)             | .73                                        |
| T stage        |                              |                                            |
| T1-T2          | Reference                    | Reference                                 |
| T3-T4          | 95.85 (44.87-204.73)         | <.01                                       |
| N stage        |                              |                                            |
| N0             | Reference                    | Reference                                 |
| N1             | 7.75 (3.65-16.47)            | <.01                                       |

15. The North American Neuroendocrine Tumors Society guidelines conclude that tumors <2 cm that are confined to the mucosa or submucosa are associated with very minimal risk of local and metastatic spread, and metastatic screening or follow-up are not recommended after local resection. In contrast, the National Comprehensive Cancer Network guidelines suggest that all patients should be screened with colonoscopy plus either abdominal/pelvic CT/MRI and endorectal ultrasound or endoscopic ultrasound.
CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Wen Cai and Weiting Ge. The first draft of the manuscript was written by Wen Cai. Jiashan Mao and Hanguang Hu check the data and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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