Endoscopic and Surgical Treatment of T1N0M0 Colorectal Neuroendocrine Tumors: A Population-Based Comparative Study

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Abstract

Background: With the rapid advances in endoscopic technology, endoscopic therapy (ET) is increasingly applied to the treatment of small (≤20 mm) colorectal neuroendocrine tumors (NETs). However, long-term data comparing ET and surgery for management of T1N0M0 colorectal NETs are lacking. The purpose of this work was to compare overall survival (OS) and cancer-specific survival (CSS) of such patients with ET or surgery.

Methods: Patients with T1N0M0 colorectal NETs were identified within the Surveillance Epidemiology and End Results (SEER) database (2004-2016). Demographics, tumor characteristics, therapeutic methods, and survival were compared. Propensity score matching (PSM) was used 1:3 and among this cohort, Cox proportional hazards regression models were performed to evaluate correlation between treatment and outcomes.

Results: Of 4487 patients with T1N0M0 colorectal NETs, 1125 were identified in the matched cohort, among whom 819 (72.8%) underwent ET and 306 (27.2%) underwent surgery. There was no difference in the 5-year and 10-year OS and CSS rates between the 2 treatment modalities. Likewise, analyses stratified by tumor size and site showed that patients did not benefit more from surgery compared with ET. Moreover, multivariate analyses found no significant differences in OS [Hazard Ratio (HR) = 0.857, 95% Confidence Interval (CI): 0.513–1.431, P = 0.555] and CSS (HR = 0.925, 95% CI: 0.282–3.040, P = 0.898) between the 2 groups. Similar results were observed when comparisons were limited to patients with different tumor size and site.

Conclusions: In this population-based study, patients treated endoscopically had comparable long-term survival compared with those treated surgically, which demonstrates ET as an alternative to surgery in T1N0M0 colorectal NETs.

Background

Neuroendocrine tumors (NETs), traditionally known as carcinoid tumors, are heterogeneous neoplasms originating from the dispersive neuroendocrine system[1]. NETs involving the digestive tract account for about two-thirds of all NETs[2]. However, colorectal NETs are rare, taking up a small proportion of these tumors[3]. The incidence of colorectal NETs has been increasing worldwide in recent decades, partly owing to advances in diagnostic technology, increased screening colonoscopy, and rising awareness of doctors[4–6]. The latest data show that colonic and rectal NETs are diagnosed at rates of 0.3 and 1.1 per 100,000 population in the United States, respectively[2, 7]. Compared with the more common colorectal adenocarcinomas, most colorectal NETs have a relatively slow speed of growth and behave less aggressively[3]. In general, early-stage colorectal NETs are connected with a quite positive long-term outcome[1]. For stage I (T1N0M0) colorectal NETs, there is a roughly 97% 5-year survival, and the 10-year survival rates of the colonic and rectal NETs are 92% and 91%, respectively[8, 9].

Surgery is regarded as the mainstay of treatment for localized colorectal NETs. In recent years, endoscopic therapy (ET) has gradually become a safe and effective alternative for the removal of these lesions through colonoscopy[10, 11], which contributes to minimal invasiveness, low health care cost, rapid postoperative recovery, and favorable patient tolerance[12]. The majority of rectal NETs are often discovered accidentally during colonoscopy, therefore they are characterized by tiny (less than 10 mm), low-grade and local lesions with low risk of metastasis[6, 13, 14]. According to the National Comprehensive Cancer Network (NCCN) guidelines, ET is recommended for rectal NETs smaller than 20 mm in size and confined within the mucosal or submucosal (T1) layer[15]. However, some scholars argue that R0 resection cannot be achieved only by local resection for rectal neoplasms with a diameter of 10–20 mm because the risk of metastasis and the degree of malignancy increase markedly when the tumors grow more than 10 mm[16–18]. As for NETs occurring in the colon, endoscopic resection can be performed if tumors are less than 20 mm with depth of invasion not reaching the muscularis propria based on the consensus of Chinese experts[19]. Furthermore, Al Natour et al. recently suggested that endoscopic resection might be suitable for patients with early colonic NETs located in mucosa and less than 10 mm[20]. This is further supported by the fact that intramucosal colonic NETs with a small diameter are linked to a low lymph node metastasis rate (4%)[20].

Although significant progress has been made in ET, the management of T1N0M0 colorectal NETs remains a controversial area due to limited studies directly comparing ET and surgery[21]. Besides, no randomized controlled trial comparing survival prognosis between these two treatments has been performed. In this study, we analyzed the Surveillance Epidemiology and End Results (SEER) database to evaluate 5-year and 10-year overall survival (OS) and cancer-specific survival (CSS) of patients with T1N0M0 colorectal NETs after treatment by endoscopy or surgery, as well as to compare OS and CSS in the light of tumor size and site, and to determine independent predictors of OS and CSS.

Methods

Study population and data source

This project was exempt from review by the institutional review board. We used the SEER database to analyze survival prognosis in the endoscopic and surgical treatment of patients with T1N0M0 colorectal NETs from 2004 through 2016. The SEER program of the National Cancer Institute (NCI) collects information including patient demographics, tumor characteristics, cancer-associated treatment detail, and follow-up for survival outcomes from multiple geographic areas, which now comprises nearly 34% of the overall U.S. population[22] (http://www.seer.cancer.gov). Data were extracted from the database using SEER*Stat software (version 8.3.6; NCI, Bethesda, MD). We identified subjects of primary colorectal NETs (site codes, C18.0, C18.2-C18.9, C19.9, and C20.9) with specific histologic subtypes based on International Classification of Diseases for Oncology, Third Edition (ICD-O-3) (histology codes, 8150–8157, 8240–8246, and 8249), and T1N0M0 disease. In the light of the eighth edition of the American Joint Committee on Cancer (AJCC) tumor staging system, T1 referred to the tumor that invades the lamina propria or submucosa and is no more than 20 mm[23]. Then, patients diagnosed with poorly or

undifferentiated grade tumors, with a diagnosis reported solely by an autopsy or death certificate, with a history of other primary malignancy or chemotherapy, without undergoing endoscopic or surgical therapy, and with survival less than one month were excluded from the research.

All patients' relevant demographic data (age, sex, race, insurance, and marital status), tumor characteristics (tumor location, depth of invasion, tumor size, AJCC staging, and tumor grade), type of operation performed, survival information during follow-up through December 31, 2016, were abstracted. Treatment modality was categorized into endoscopic (codes: 10–14 and 20–28) and surgical resection (codes:30–31, 40, 50, 60, 70, and 80) groups according to the surgery codes proposed by the American College of Surgeons Commission on Cancer' s Facility Oncology Registry Data System[24]. Additionally, the continuous variable of tumor size was divided into two sets: smaller than 10 mm and 10–20 mm.

Statistical analysis

The study sample was classified into two categories in terms of treatment: those treated only endoscopically and those treated by surgical excision. The frequencies and percentages of the categorical variables were computed for the features of patient and tumor. Comparisons of categorical data between treatment groups were completed using chi-square test or Fisher's exact test. The propensity score matching (PSM) was constructed to regulate the non-random allocation of patients. Patients were matched 1:3 into endoscopic and surgical groups. The six covariates applied to match were as follows: age, marital status, tumor site, tumor diameter, depth of tumor infiltration, and differentiation grade. After PSM, chi-square test was utilized to evaluate the differences of categorical clinicopathological characteristics between the two groups.

For patients with sufficient follow-up, we compared overall and cancer-specific 5- and 10-year survival rates between ET and surgery. Death attributed to colorectal NETs was defined as CSS. We employed the Kaplan-Meier method to generate survival curves and compared them with the log-rank analysis. And multivariate Cox regression analysis was conducted to determine independent prognostic variables on outcomes. The results were showed as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). In addition, we performed subgroup analysis to determine whether operation type had different effects on survival in various subgroups.

Data analyses including chi-square test and multivariable Cox regression were conducted using SPSS Statistics software 24.0 (IBM Corporation, Chicago, IL). GraphPad Prism 8.0 (San Diego, CA, USA) was utilized for the Kaplan-Meier survival curves and log-rank test. Besides, PSM was implemented in R software 3.6.2 (https://www.rproject.org/). For all analyses, comparative differences indicated statistically significance when the two-sided P-value < 0.05.

Results

Demographics

A total of 4487 cases diagnosed with T1N0M0 colorectal NETs were selected for entering in the study. Of these patients, 4149 (92.5%) accepted ET and 338 (7.5%) received surgery. Among the unmatched cohort, surgery was employed more frequently in older patients (≥ 60 years: 34.0% vs. 27.1%, P = 0.007) with unmarried status (32.0% vs. 28.3%, P = 0.000), in those with colonic disease (58.9% vs. 9.3%, P = 0.000), in tumors with larger lesions (10–20 mm: 33.4% vs. 13.9%, P = 0.000), in neoplasms with submucosal invasion (57.4% vs. 37.6%, P = 0.000), and in moderately differentiated cancers (13.0% vs. 6.3%, P = 0.000). PSM was then carried out and a new endoscopic (n = 819) and surgical (n = 306) cohort were generated. After pairing, all variables of both treatment cohorts were balanced, showing no significant difference. The demographic and clinicopathological features of the unmatched and matched cohorts are provided in Table 1.

Table 1
Comparison of baseline characteristics between patients with T1N0M0 colorectal neuroendocrine tumors undergoing endoscopic therapy (ET) and surgery in unmatched and matched cohort

Characteristic	Before matching			After matching		
	ET (n = 4149)	Surgery (n = 338)	p value	ET (n = 819)	Surgery (n = 306)	p value
Age,%			0.007			0.145
60 years	3023 (72.9)	223 (66.0)		598 (73.0)	210 (68.6)	
≥ 60 years	1126 (27.1)	115 (34.0)		221 (27.0)	96 (31.4)	
Gender,%			0.389			0.503
Male	2016 (48.6)	156 (46.2)		385 (47.0)	137 (44.8)	
Female	2133 (51.4)	182 (53.8)		434 (53.0)	169 (55.2)	
Race, %			0.438			0.704
White	2310 (55.7)	194 (57.4)		443 (54.1)	172 (56.2)	
Black	943 (22.7)	81 (24.0)		218 (26.6)	74 (24.2)	
Other	896 (21.6)	63 (18.6)		158 (19.3)	60 (19.6)	
Site of cancer,%			0.000			0.151
Colon	386 (9.3)	199 (58.9)		242 (29.5)	104 (34.0)	
Rectum	3763 (90.7)	139 (41.1)		577 (70.5)	202 (66.0)	
Histological grade,%			0.000			0.201
Well-differentiated	1656 (39.9)	143 (42.3)		362 (44.2)	138 (45.1)	
Moderately-differentiated	263 (6.3)	44 (13.0)		54 (6.6)	29 (9.5)	
Unknown	2230 (53.7)	151 (44.7)		403 (49.2)	139 (45.4)	

Other: American Indian, Alaska Native, Asian/Pacific Islander, unknown; NOS: Not otherwise specified; ET: Endoscopic therapy.

Characteristic	Before matching			After matching		
	ET (n = 4149)	Surgery (n = 338)	p value	ET (n = 819)	Surgery (n = 306)	p value
Tumor size,%			0.000			0.330
≤10 mm	3572 (86.1)	225 (66.6)		620 (75.7)	223 (72.9)	
10–20 mm	577 (13.9)	113 (33.4)		199 (24.3)	83 (27.1)	
Submucosal involvement,%			0.000			0.856
No submucosal involvement	1093 (26.3)	50 (14.8)		130 (15.9)	45 (14.7)	
With submucosal involvement	1562 (37.6)	194 (57.4)		442 (54.0)	170 (55.6)	
T1,NOS	1494 (36.0)	94 (27.8)		247 (30.2)	91 (29.7)	
Insurance,%			0.949			0.976
Insured	3136 (75.6)	256 (75.7)		635 (77.5)	237 (77.5)	
Uninsured/Unknown	1013 (24.4)	82 (24.3)		184 (22.5)	69 (22.5)	
Marital status,%			0.000			0.655
Married	2350 (56.6)	208 (61.5)		519 (63.4)	188 (61.4)	
Unmarried	1174 (28.3)	108 (32.0)		243 (29.7)	99 (32.4)	
Unknown	625 (15.1)	22 (6.5)		57 (7.0)	19 (6.2)	

Other: American Indian, Alaska Native, Asian/Pacific Islander, unknown; NOS: Not otherwise specified; ET: Endoscopic therapy.

Comparison Of Et And Surgery Outcomes

The median follow-up time was 62 months in the endoscopic group and 67 months in the surgical group. These patients failed to reach the median survival duration. The overall OS and CSS rates were similar at both 5 and 10 years of follow-up between the two groups [5-year OS (94.8% vs. 93.4%, P = 0.2388), 10-year OS (90.9% vs. 88.5%, P = 0.2388), 5-year CSS (99.3% vs. 97.5%, P = 0.2161), 10-year CSS (98.7% vs.

97.5%, P = 0.2161)] (Table 2). When subjects were categorized into subgroups according to tumor size, patients with tumors < 10 mm in size were found to have no difference between the two subgroups with regards to the 5-year and 10-year OS [5-year OS (95.8% vs. 93.9%, P = 0.3926) and 10-year OS (91.9% vs. 90.7%, P = 0.3926)] and CSS [5-year CSS (99.8% vs. 98.1%, P = 0.1014) and 10-year CSS (99.4% vs. 98.1%, P = 0.1014)]. Similar outcomes were observed in thoses with cancers 10 to 20 mm [5-year OS (92.0% vs. 91.7%, P = 0.4714), 10-year OS (87.7% vs. 83.8%, P = 0.4714), 5-year CSS (97.8% vs. 95.8%, P = 0.8229), 10-year CSS (96.8% vs. 95.8%, P = 0.8229)]. Considering the different biological characteristics of NETs of the colon and rectum, we further performed a subgroup analysis based on the tumor site. In those with colonic NETs, the OS rate was significantly higher in patients treated with ET both at 5 (95.1% vs. 88.1%, P = 0.0187) and 10 years (93.2% vs. 82.3%, P = 0.0187) of follow-up. However, there was no difference in treatment-related CSS rate at 5 and 10 years [5-year CSS (99.2% vs. 95.9%, P = 0.4497) and 10-year CSS (98.2% vs. 95.9%, P = 0.4497)]. In those with rectal NETs, comparable 5-year and 10-year OS and CSS rates were noted when ET was compared to surgical treatment [5-year OS (94.8% vs. 96.1%, P = 0.6918), 10-year OS (89.8% vs. 91.7%, P = 0.6918), 5-year CSS (99.4% vs. 98.3%, P = 0.3281), 10-year CSS (99.0% vs. 98.3%, P = 0.3281)]. Kaplan-Meier curves again disclosed no significant discrepancy in overall OS (P = 0.2388) and CSS (P = 0.2161) between the two therapy methods (Fig. 1A-1B). Likewise, our analyses stratified by tumor size and site demonstrated that patients did not benefit more from surgery compared with ET (Fig. 2A-2D, 3A-3D).

Table 2
Long-term outcomes of patients with T1N0M0 colorectal neuroendocrine tumors in different groups

Variable	ET	Surgery	p value
Estimated 5-year OS rate, %			
all T1 tumor	94.8	93.4	0.2388
≤10 mm tumor	95.8	93.9	0.3926
10–20 mm tumor	92.0	91.7	0.4714
colonic tumor	95.1	88.1	0.0187
rectal tumor	94.8	96.1	0.6918
Estimated 5-year CSS rate, %			
all T1 tumor	99.3	97.5	0.2161
≤10 mm tumor	99.8	98.1	0.1014
10–20 mm tumor	97.8	95.8	0.8229
colonic tumor	99.2	95.9	0.4497
rectal tumor	99.4	98.3	0.3281
Estimated 10-year OS rate, %			
all T1 tumor	90.9	88.5	0.2388
≤10 mm tumor	91.9	90.7	0.3926
10–20 mm tumor	87.7	83.8	0.4714
colonic tumor	93.2	82.3	0.0187
rectal tumor	89.8	91.7	0.6918
Estimated 10-year CSS rate, %			
all T1 tumor	98.7	97.5	0.2161
≤10 mm tumor	99.4	98.1	0.1014
10–20 mm tumor	96.8	95.8	0.8229
colonic tumor	98.2	95.9	0.4497
rectal tumor	99.0	98.3	0.3281
OS: Overall survival; CSS: Cancer-specific survival; ET: Endoscopic therapy.			

Multivariable Predictors Of Survival

Table 3 displays the multivariate analysis of OS and CSS. From the results of Cox regression models, patients who treated with ET enjoyed a similar risk of overall death (HR = 0.857, 95% CI: 0.513–1.431, P = 0.555) and cancer-specific death (HR = 0.925, 95% CI: 0.282–3.040, P = 0.898) compared with surgical resection group after adjustment for potential confounders. In the OS cohort, we identified age, gender, race, marital status, histological grade, and tumor size as independent prognostic indicators of survival. In the CSS cohort, patients aged 60 years or older, moderately differentiated NETs, and tumors of 10–20 mm were found to be predictors of increased hazard of tumor-specific death.

Table 3
Multivariate cox regression analysis of OS and CSS in patients with T1N0M0 colorectal neuroendocrine tumors

Variable	OS		CSS	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age (years)				
60	Reference		Reference	
≥ 60	3.814 (2.311–6.296)	0.000	3.921 (1.231–12.490)	0.021
Gender				
Male	Reference		Reference	
Female	0.586 (0.356–0.963)	0.035	0.844 (0.276–2.579)	0.766
Race				
White	Reference		Reference	
Black	1.102 (0.641–1.894)	0.725	1.593 (0.474–5.347)	0.451
Other	0.241 (0.074–0.787)	0.018	0.372 (0.043–3.218)	0.369
Site of cancer				
Rectum	Reference		Reference	
Colon	1.227 (0.744–2.024)	0.422	2.305 (0.715–7.431)	0.162
Histological grade				
Well-differentiated	Reference		Reference	
Moderately-differentiated	2.645 (1.192–5.868)	0.017	16.073 (2.842–90.905)	0.002
Unknown	0.678 (0.374–1.228)	0.199	2.121 (0.393–11.438)	0.382
Treatment				
Surgery	Reference		Reference	

OS: Overall survival; CSS: Cancer-specific survival; CI: Confidence interval; Other: American Indian, Alaska Native, Asian/Pacific Islander, unknown; NOS: Not otherwise specified; ET: Endoscopic therapy.

Variable	OS		CSS	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
ET	0.857 (0.513–1.431)	0.555	0.925 (0.282–3.040)	0.898
Tumor size (mm)				
≤10	Reference		Reference	
10–20	1.797 (1.094–2.953)	0.021	4.110 (1.288–13.113)	0.017
Submucosal involvement				
NO submucosal involvement	Reference		Reference	
With submucosal involvement	1.022 (0.497–2.102)	0.952	1.714 (0.196–14.992)	0.626
T1,NOS	0.895 (0.421–1.903)	0.773	1.914 (0.222–16.534)	0.555
Insurance				
Insured	Reference		Reference	
Uninsured/Unknown	1.240 (0.700-2.196)	0.461	0.631 (0.153–2.595)	0.523
Marital status				
Married	Reference		Reference	
Unmarried	2.402 (1.404–4.109)	0.001	1.787 (0.500-6.387)	0.372
Unknown	1.637 (0.567–4.732)	0.363	4.689 (0.841–26.150)	0.078

OS: Overall survival; CSS: Cancer-specific survival; CI: Confidence interval; Other: American Indian, Alaska Native, Asian/Pacific Islander, unknown; NOS: Not otherwise specified; ET: Endoscopic therapy.

Table 4
Overall survival and Cancer-specific survival of study subgroups in multivariable analyses

	Overall survival		Cancer-specific survival	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
ET vs surgery (reference)				
overall***	0.857 (0.513–1.431)	0.555	0.925 (0.282–3.040)	0.898
≤10 mm tumor**	0.806 (0.397–1.634)	0.549	0.313 (0.024–4.165)	0.379
10–20 mm tumor**	0.764 (0.337–1.731)	0.519	2.154 (0.319–14.526)	0.431
colonic tumor*	0.510 (0.234–1.114)	0.091	1.439 (0.200-10.341)	0.718
rectal tumor*	1.399 (0.661–2.961)	0.381	0.584 (0.089–3.812)	0.574
CI: Confidence interval; ET: Endoscopic therapy.				
***adjusted for age, gender, race, site of cancer, histological grade, tumor size, depth of tumor invasion, insurance and marital status				
**adjusted for age, gender, race, site of cancer, histological grade, depth of tumor invasion, insurance and marital status				
*adjusted for age, gender, race, histological grade, tumor size, depth of tumor invasion, insurance and marital status				
.				

Since treatment strategies might be affected by the size and site of the colorectal NETs, we further conducted subgroup analyses on the basis of tumor size and site. After controlling for potential confounding variables, there were no treatment-associated differences in OS (HR = 0.806, 95% CI 0.397–1.634, P = 0.549) or CSS (HR = 0.313, 95% CI 0.024–4.165, P = 0.379) in cases with colorectal NETs less than 10 mm in size. When patients were limited to tumors of 10–20 mm, similar results were obtained with no discrepancy in the HR between both groups for OS (HR = 0.764, 95% CI 0.337–1.731, P = 0.519) and CSS (HR = 2.154, 95% CI 0.319–14.526, P = 0.431). Similarly, we also found that the HR for OS and CSS was not significantly different between the 2 treatment modalities in patients with colonic [OS (HR = 0.510, 95% CI: 0.234–1.114, P = 0.091) and CSS (HR = 1.439, 95% CI: 0.200–10.341, P = 0.718)] and rectal [OS (HR = 1.399, 95% CI:0.661–2.961, P = 0.381) and CSS (HR = 0.584, 95% CI: 0.089–3.812, P = 0.574)] NETs.

Discussion

Although NETs of the colon and rectum are relatively rare compared to colorectal adenocarcinomas, a growing number of colorectal NETs are diagnosed at an early stage thanks in part to greater investigation

with colonoscopy. These tumors tend to progress indolently and have a satisfying prognosis[25]. The median survival duration in patients with localized NETs of the colon and rectum is 261 and 290 months, respectively[3]. Nevertheless, colorectal NETs, especially in T1N0M0 lesions, remains an elusive disease with unclear and inconsistent guidelines for selecting the optimal treatment. Currently, there are two main modalities including endoscopic and surgical procedures used in the treatment of T1N0M0 colorectal NETs, and ET provides a minimally invasive method for the removal of these lesions. Compared with surgery, ET has a stronger correlation with reduced mortality[26]. Moreover, data from previous studies have shown that ET offered a high complete resection rate (80.6% – 96.7%), a limited adverse event rate, and a low recurrence rate for colorectal NETs smaller than 20 mm in size, which further evidence that ET is a safe and effective approach for resecting T1N0M0 colorectal NETs with malignant potential[10, 27].

In the present study, we compared long-term (5-year and 10-year) outcomes of ET and surgery and identified independent prognostic factors of survival. According to our findings, there were significant differences in clinical characteristics between ET and surgery patients. ET was used more commonly in younger and married patients. Besides, the patients treated endoscopically were more likely to demonstrate smaller tumors, rectal lesions, no submucosal involvement, and well-differentiated histology. As in previous research, the prognosis was linked to age[28], marital status[29], tumor size[2], tumor site[2], and differentiation grade[1]. Since these covariates might lead to bias that disturbs the comparison of treatment strategies, PSM was employed in this study. OS and CSS were comparable at both 5 and 10 years between the 2 therapies. Similar results were noted in subgroup analyses of patients with different tumor sizes. In patients with colonic disease, the OS rate was higher in the ET group at both 5 and 10 years of follow-up in comparison to the surgery group, whereas patients undergoing ET did not differ from those receiving surgical resection regarding the 5-year and 10-year CSS. Limiting to patients with rectal lesions, there were no differences between the two groups in the 5-year and 10-year OS and CSS. Besides, we did not observe a significant difference in OS and CSS between treatment groups in the Cox proportional hazards regression models. Similar results were seen when modeling was based on different tumor size or site.

Thus far, there remains limited data comparing survival outcomes of ET and surgery for T1N0M0 colorectal NETs. Previously, one study using the SEER database[21] compared the long-term survival of 618 patients with T1N0M0 rectal carcinoid tumors diagnosed between 1998 through 2012 and discovered comparable CSS between local excision and radical surgery. However, this study did not include colonic disease. Accordingly, the same outcome that ET was related to equivalent OS and CSS was acquired in our large population-based study with a PSM cohort, and also found that therapeutic modality was not an important prognostic indicator by multivariate analysis. We also found that increasing age, higher tumor grade, and tumor size between 10–20 mm were predictive of poorer OS and CSS. Yet, gender, as well as race and marital status, was independently associated with OS.

The status of regional lymph nodes is an important factor in the choice of endoscopic or surgical treatment. Studies have shown that colorectal NETs smaller than 10 mm had a low prevalence of metastasis (colon: 4%; rectum: <3%), which demonstrated that ET was sufficient for these small

tumors[20, 21]. This is in accordance with our result that ET and surgery were associated with similar survival in patients with tumors less than 10 mm. However, lymph node metastasis occurs more frequently in colorectal NETs varying from 10 mm to 20mm[30]. Additionally, Konishi et al.[17] reported that if patients with colorectal NETs had lymph node or distant metastases, their survival rate was similar to those with colorectal adenocarcinomas. Tumors of intermediate size (10–20 mm) should be treated as adenocarcinomas by aggressive surgical resection with regional lymphadenopathy[21, 31]. On the contrary, some research suggested that endoscopic resection was reasonable to remove these larger lesions as they were considered indolent in nature[10, 32, 33], which is consistent with our finding that survival rates following ET and surgery were equivalent in patients with tumors of 10–20 mm in size. Although our data favor safe ET for T1N0M0 colorectal NETs regardless of tumor size, endoscopic ultrasonography (EUS) should be conducted to evaluate the tumor diameter, the depth of intestinal wall invasion and local lymph node status prior to ET.

The current NCCN guidelines indicate that T1N0M0 rectal disease can be safely removed through endoscopy[15], which is supported by our study that no significant difference was observed in survival between rectal tumor patients who underwent ET and those who received surgery. Of note, patients with colonic NETs who treated surgically did not confer extra survival benefits. Our finding appears to be inconsistent with the recommendations of management guidelines for colonic NETs[15]. For example, a partial colectomy with regional lymphadenectomy is usually advised for localized colonic NETs on the basis of the NCCN guidelines. However, all of the patients included in this study were at stage T1N0M0, the earliest stage of the disease with the lowest degree of malignancy. What's more, in a report by Landry et al.[8, 9], the survival rate was similar between early NETs of the colon and rectum, further revealing that the malignant degree of early tumors in both sites has little difference. Although it has not become a formal proposal in western countries, T1N0M0 colonic NETs can be managed with ET according to the consensus of Chinese experts[19]. Thus, we have reason to believe that ET is appropriate for T1N0M0 colonic NETs, similar to the treatment of T1N0M0 rectal NETs.

Tumor size is not only a major predictor of regional spread but also a predictive factor of survival[2]. In line with the previous reports[1, 20], our multivariate analysis disclosed that increasing tumor size was an independent predictor connected with the incremental risk of overall and cancer-specific mortality. Although it is generally acknowledged that the depth of wall penetration is associated with prognosis[30], no correlation between them was found in our study, which may be the result of unknown infiltration extent in 338 (30.0%) cases. Thus, further studies that evaluate the prognostic value of invasive depth are warranted.

There are several limitations to our study that deserve discussion. On account of its retrospective nature, there is affected by selection bias and confounding factors. Data on patient comorbidities is not available in the SEER database. In general, patients with increased comorbidities tend to undergo ET as a result of its less invasiveness. It is worth noting that although higher comorbidity can potentially lead to a bias against ET, there was no difference in CSS between these 2 treatments. Therefore, the absence of comorbidity information should not influence our overall results. Second, the SEER database does not

provide data regarding several important prognostic factors (lymphovascular invasion and resection margin), treatment-related complications, means of endoscopic resection. Randomized, controlled trials can adequately address this limitation. Moreover, the use of targeted therapy is not captured by this database. However, patients with T1N0M0 colorectal NETs scarcely receive this treatment, which most likely does not impact our results. In addition, the SEER database records only original therapy and does not document patients in whom ET failed. Lastly, there was also no information on disease recurrence. Despite these issues, the SEER database is a large-scale database with detailed and accurate data recording. We made an attempt to reduce potential bias by performing a PSM and adjusting the HR for the influence of ET on survival.

Conclusion

In summary, the results of our study demonstrate comparable long-term survival outcomes between ET and surgery in patients with T1N0M0 colorectal NETs, which supports that ET is a reasonable alternative to surgery for the treatment of T1N0M0 colorectal NETs.

Abbreviations

endoscopic therapy
ET, neuroendocrine tumors:NETs, overall survival:OS, cancer-specific survival:CSS, Surveillance Epidemiology and End Results database:SEER database, propensity score matching:PSM, Hazard Ratio:HR, 95% Confidence Interval:95% CI, National Comprehensive Cancer Network:NCCN, National Cancer Institute:NCI, American Joint Committee on Cancer:AJCC.

Declarations

Acknowledgments

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Availability of data and materials

The data were abstracted from the Surveillance, Epidemiology, and End Results (SEER) database. This is an open database. (https://seer.cancer.gov).

Authors' contributions

HLZ, SZ and KJ designed the study. HLZ and WW performed data mining. JZ and CMZ analyzed the data. HLZ, SZ and RYT drafted the initial manuscript. JK and LM contributed to the revision of the

manuscript . All authors read and approved the final manuscript.

Ethics approval and consent to participate

Institutional review board approval was not needed for this study as it utilized publically available data.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to declare.

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Figures

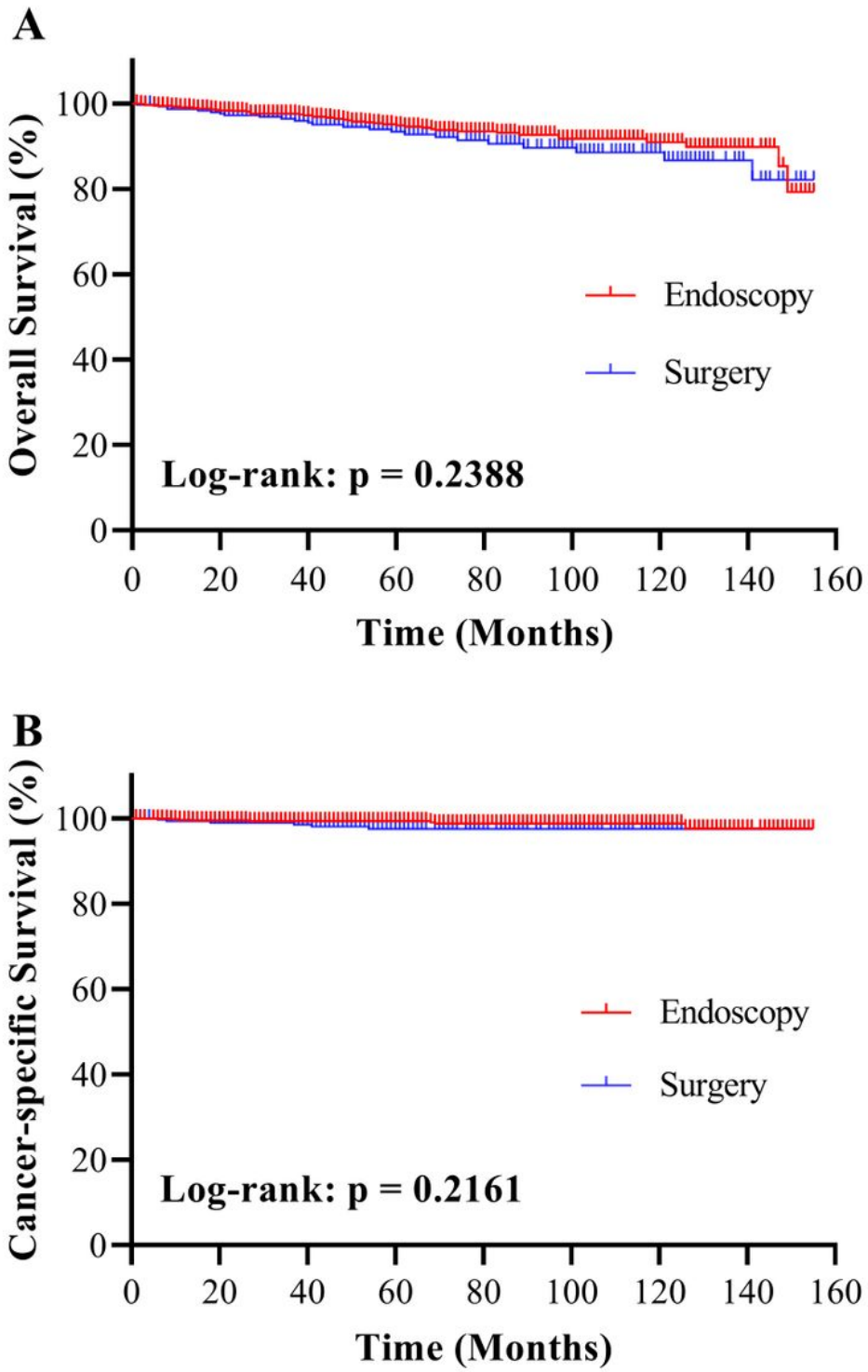

Figure 1

1 Kaplan-Meier survival curves comparing endoscopic therapy and surgery for patients with T1N0M0 colorectal neuroendocrine tumors. (A) Overall survival; (B) Cancer-specific survival.

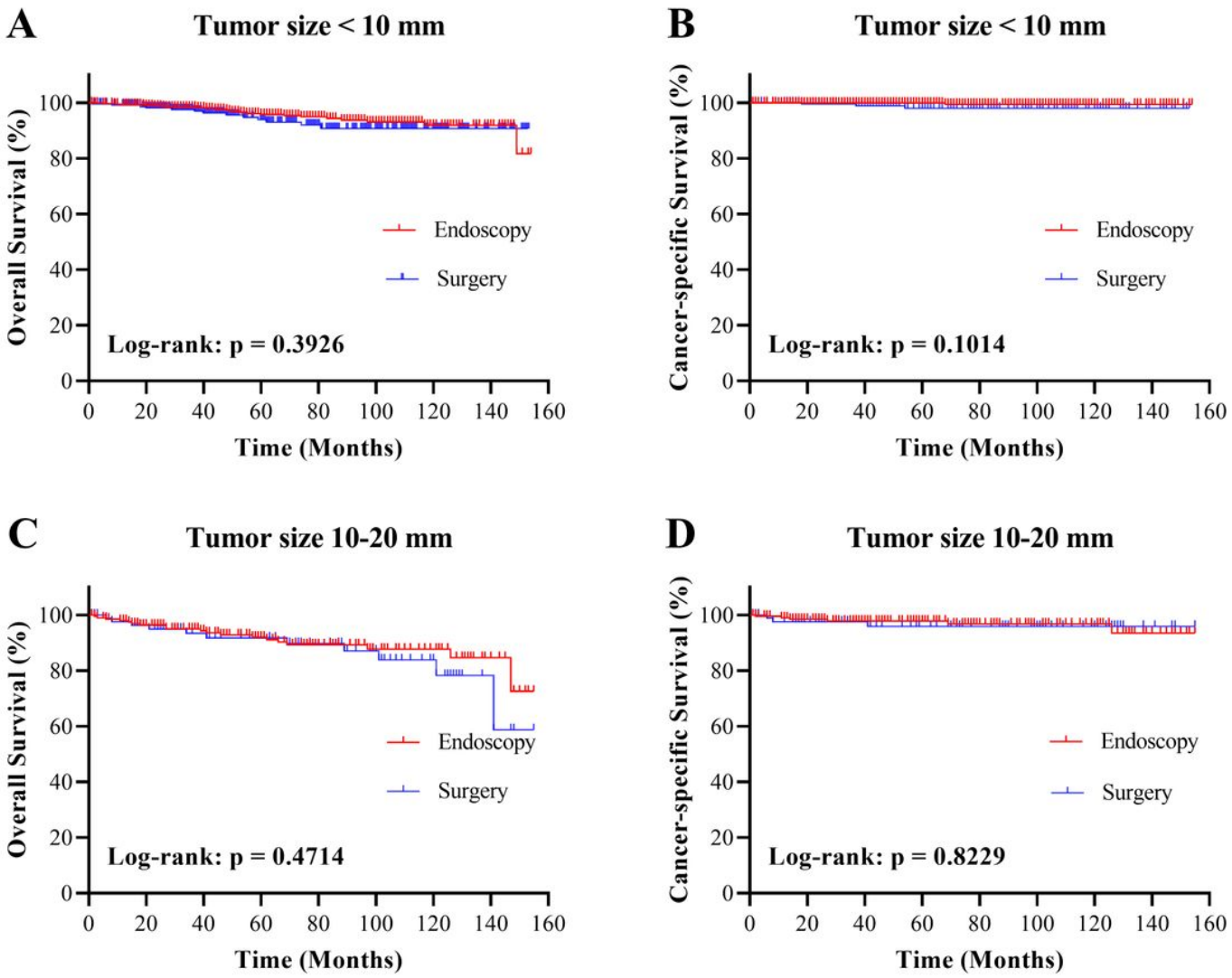

Figure 2

Kaplan-Meier survival curves for (A) overall survival and (B) cancer-specific survival in patients with tumors less than 10 mm undergoing endoscopic therapy or surgery. Kaplan-Meier survival curves for (C) overall survival and (D) cancer-specific survival in patients with tumors 10-20 mm undergoing endoscopic therapy or surgery.

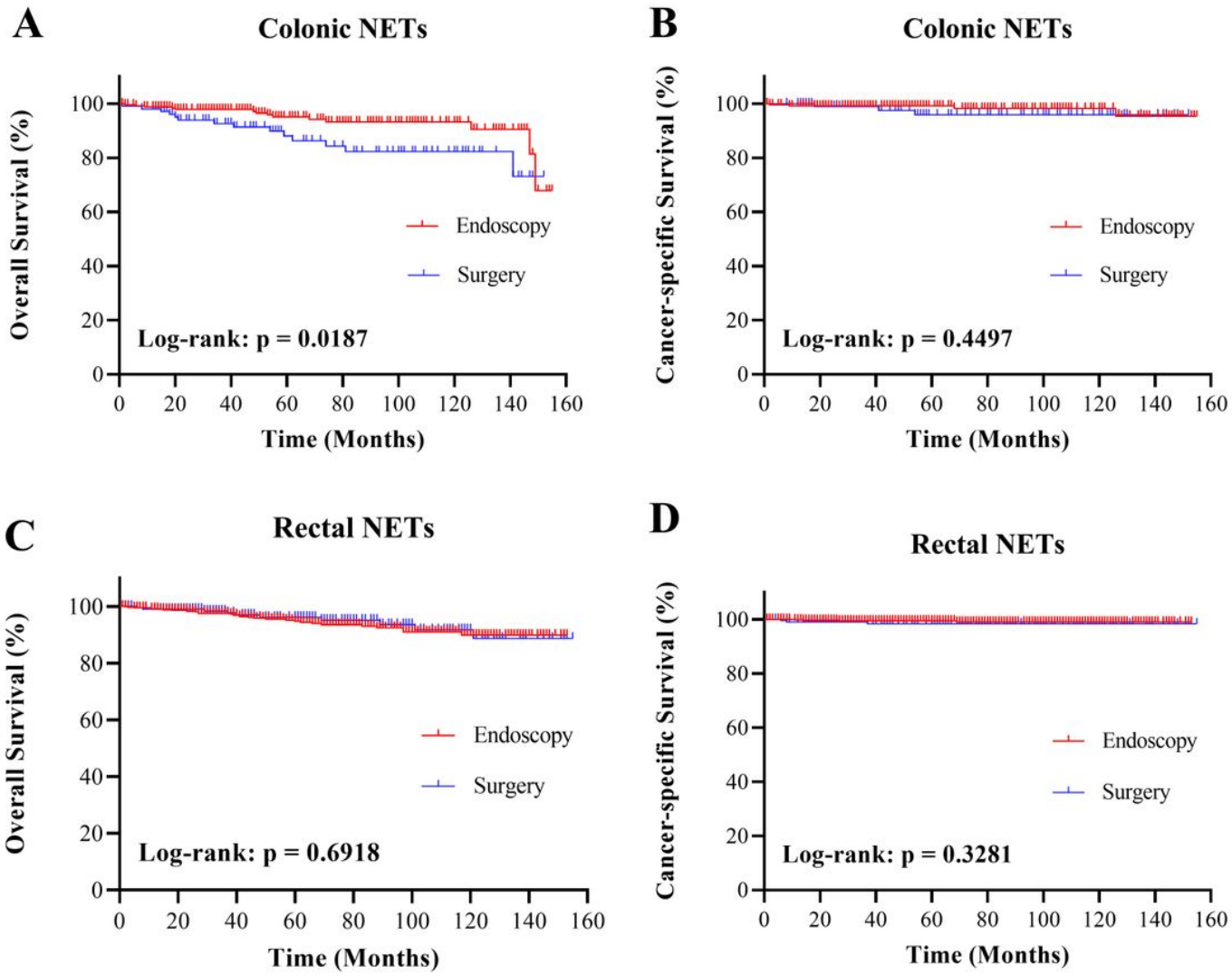

Figure 3

Kaplan-Meier survival curves for (A) overall survival and (B) cancer-specific survival in patients with colonic tumors undergoing endoscopic therapy or surgery. Kaplan-Meier survival curves for (C) overall survival and (D) cancer-specific survival in patients with rectal tumors undergoing endoscopic therapy or surgery.