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Retrospective Study
Prognostic impact of examined lymph nodes and survival analysis of patients with appendiceal neuroendocrine tumors

Rui Du, Jiang-Wei Xiao

Abstract
BACKGROUND
Prognostic of patients with appendiceal neuroendocrine tumors (ANETs) is related to lymph node (LN) and other factors. But it is unclear how examined lymph nodes (ELN) impacting on survival.

AIM
To determine the related factors affecting the cancer-specific survival (CSS) of patients with ANET and to evaluate the impact of ELN on survival.

METHODS
A total of 4583 ANET patients were analyzed in the Surveillance, Epidemiology, and End Results (SEER) database. Univariate survival analysis was used to identify factors related to survival and the optimal ELN and lymph node ratio (LNR) have been founded by the Kaplan–Meier method. The survival difference was determined by CSS.

RESULTS
Except for sex, most of the factors, such as age, year, race, grade, histological type, stage, tumor size, ELN, LNR, and surgery type, were associated with prognosis. The 3-, 5-,
and 10-year CSS rates of ANET patients were 91.2%, 87.5, and 81.7%, respectively (median follow-up period of 31 months and range of 0-499 months). There was no survival difference between the two surgery types, namely, local resection and colectomy or greater, in both stratifications of tumor size ≥ 2 cm (P=0.523) and < 2 cm (P = 0.068). In contrast to patients with a tumor size < 2 cm, size ≥ 2 cm were more likely to have LN metastasis ($\chi^2=378.16, P < 0.001$). The optimal number of ELN was more than 11, 7, and 18 for all patients, node-negative patients, and node-positive patients, respectively. CSS rates of patients with larger ELN were significantly improved (≤ 10 vs ≥ 11, $\chi^2 = 20.303, P < 0.001$; ≤ 6 vs ≥ 7, $\chi^2 = 11.569, P < 0.001$; ≤ 17 vs ≥ 18, $\chi^2 = 21.990, P < 0.001$; respectively). ANET patients with LNR values ≤ 0.16 were more likely to have better survival than values of 0.17-0.48 ($\chi^2 = 48.243, P < 0.001$) and 0.49-1 ($\chi^2 = 168.485, P < 0.001$).

CONCLUSION
ANET ≥ 2 cm are more likely to have LN metastasis. At least 11 ELN to better evaluate the prognosis. For patients with positive LN metastasis, 18 or more LNs needs to be detected and lower LNR values (LNR ≤ 0.16) indicate a better survival prognosis.

Key Words: Appendiceal neoplasm; Neuroendocrine tumors; Carcinoid tumor; Lymph node dissection; Lymph node ratio; Survival analysis

Core Tip: This study aimed to explore factors that have an influence on survival of patients with appendiceal neuroendocrine tumors. We found out the optimal number of examined lymph nodes that could acquire best survival for patients with appendiceal neuroendocrine tumors in different lymph node status. Further more, lymph node ratio take both examined lymph nodes and positive lymph nodes into account. We also find out the optimal value of lymph node ratio that could acquire best survival for node-positive patients.
INTRODUCTION

Carcinoid tumors were first described by Oberndorfer[1] in 1907, and neuroendocrine tumor (NET) were first described by Lubarsch[2] in 1888. NET are mainly found within the gastrointestinal tract and historically known as carcinoid tumors. NET occur in multiple sites throughout the body[3]. Gastrointestinal NET are most common in the stomach, small intestine, and pancreas, and their incidence has been reported to be steadily increasing in recent years[4]. The Surveillance Epidemiology and End Results (SEER) database estimates 3.56 cases of gastrointestinal NET per 100,000 individuals each year[5]. Appendiceal carcinoids that is appendiceal neuroendocrine tumors (ANETs) are considered a subtype of midgut NET[6], which are the most common tumors accounts for almost 60% of all appendiceal tumors[7, 8]. Most ANETs are found via pathological examination after appendectomy. According to a retrospective study, 29 of 13,863 (0.2%) appendectomy specimens in 10 years were histopathologically NETs[7]. Another study has revealed that 17 (0.27%) of the 6369 patients who underwent appendectomy had ANETs[9].

For prognosis, a previous study has shown that the 5-year overall survival (OS) of all gastrointestinal NET is 67.2% in a cohort that included 73,782 patients[10]. Another study has shown that the median survival duration is 41 months for patients with gastrointestinal NET and 5-year and 10-year OS rates of 39.4% and 18.1%, respectively[11]. In comparison, ANET has a better prognosis than gastrointestinal NET[12]. The 10-year OS has been reported to be as high as 95% (53 of 56)[13]. ANET survival is primarily determined by tumor grade and stage[14]. In 2001, an analysis of 619 cases with ANETs using Cox multivariate regression showed that age, stage, sex, and primary appendix localization are independent predictors of survival[15]. A retrospective study has shown that the lymph node (LN) status of ANET is related to survival[16]. However, it remains unclear whether the number of LNIs detected and the positive rate are related to the prognosis.

So far, there hasn’t detail survival rate of patient with ANET, especially the survival rates related to different disease stages. Further, there are clinic cases.
diagnosed ANET preoperatively. The issue is what type of surgery should be chosen and how many LNs should be resected for optimal survival in this situation. The purpose of the present study is to determine the related factors that affect the cancer-specific survival (CSS) of ANET and the impact of the number and positive rate of LN detection on survival and prognosis. This study also investigated whether the survival prognosis is related to tumor size, scope of resection and other factors.

MATERIALS AND METHODS

Patients and data collection

Data were collected from the SEER database. A total of 14,920 cases of appendectomy were extracted by anatomical site, and 5808 cases of NETs or carcinoid tumors were identified by the 3rd edition of the International Classification of Diseases for Oncology. A total of 1002 cases of nonprimary and nonfirst primary appendiceal tumors were excluded. Ultimately, 4583 cases with ANET were included.

Variables

The following variables were reviewed: Age (age of diagnosis), year (year of diagnosis), race, sex, grade (well differentiated, moderately differentiated, poorly differentiated, and undifferentiated), histological type (9 categories), tumor size (reclassified into ≤ 2 cm and > 2 cm), and stage (patients were restaged according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system. “T stage”, namely, Tx, Tis, T1 (T1a and T1b), T2, T3, and T4 (T4a, T4b and T4). For “N stage”, the data variables (N0, N1, N2 and Nx) of the N status were reclassified into N0, N1, and missing categories. The M status in the database was transformed into the standard “M stage” by the 7th edition of AJCC, and the M0 and M1 (M1a, M1b and M1) data variables were reclassified into M0 and M1 categories. The stage status of the disease was modified to stage I-IV. Surgery types were reclassified into local resection and colectomy or greater. Examined lymph nodes (ELN) is the exact number of LNs detected of patients. “LNR” (lymph node ratio) is the lymph node positive rate, which is calculated by the number of positive LNs divided by the number of ELN. Survival months was defined as the
interval from the date of diagnosis to the date of death. CSS was the primary vital status (dead attributable to the cancer) in this study.

**Statistical analysis**

Data were entered into Excel data sheets from the SEER database and then analyzed with SPSS 18.0 (IBM, Armonk, NY, USA) statistics software for Windows. Figures were created using GraphPad Prism software version 7.00 (San Diego, CA, USA). Continuous variables are expressed as the mean ± SD. Categorical data are expressed as absolute values or fractions. The Cox proportional hazards model was applied to assess the prognostic factors associated with survival, presenting hazard ratios (HR) and 95% confidence intervals (CI). The CSS survival curves were plotted via the Kaplan-Meier method and the log-rank test. \( P < 0.05 \) was considered statistical significance. Continuous variables were also converted into categorical variables. X-tile software version 3.6.1 (Yale University, New Haven, CT, USA) was used to determine the optimal cutoff points of ELN and LNR\(^ {17} \).

**RESULTS**

**Demographic and clinicopathologic characteristics**

As shown in Table 1, 4583 patients were included from 1975 to 2016. 57% were female, and the mean age was 44.59 years. White people were the majority race. There were 4 histopathological grades according to the degrees of differentiation, and 72.6% were well differentiated. For tumor size, the mean was 17.56 mm. Most patients were at an earlier stage in terms of T, N, and M stage, and 57.36% were at stage I. On average, 16.5 LNs were examined, and the mean LNR was 0.26. The mean interval from diagnosis to the cutoff date was 64.57 months.

**Univariate analysis of Cox proportional hazard model**

The continuous variables were transformed into classified variables. In particular, age, LNR, and ELN were divided into subsections by the cutoff values found with X-tile software\(^ {17} \). Age was divided into three levels as follows: ≤ 40 years old, 41-65 years old, and ≥ 66 years old. Patients were divided into two groups according to the ELN cutoff
points. All node-positive patients were divided into three levels according to LNR cutoff points as: $0 < \text{LNR} \leq 0.16$, $0.17 \leq \text{LNR} \leq 0.48$, and $0.49 \leq \text{LNR} \leq 1$. Histological types with few patients were ignored. For the stage and grade, we clustered them into a dichotomy as: Grade 1+2 and grade 3+4; and stage I+II and stage III+IV. CSS was significantly different between the groups for each variable by Log-rank test.

In the univariate analysis, age $\geq 66$ years (HR 16.14, 95% CI 11.08-23.52, $P < 0.001$; reference: $\leq 40$ years), diagnosis in 1991-2000 (HR 4.72, 95% CI 2.51-8.85, $P < 0.001$; reference: 1975-1980), black people (HR 1.58, 95% CI 1.20-2.08, $P = 0.02$; reference: White people), females (HR 1.02, 95% CI 0.85-1.23, $P = 0.80$; reference: Male), grade 3+4 (HR 19.14, 95% CI 13.63-26.87, $P < 0.001$; reference: Grade 1+2), large cell neuroendocrine carcinoma (HR 14.45, 95% CI 10.30-20.27, $P < 0.001$; reference: Carcinoid tumor), tumor size $> 2$ cm (HR 8.54, 95% CI 5.99-12.17, $P < 0.001$; reference: $\leq 2$ cm), stage III+IV (HR 17.12, 95% CI 11.78-24.87, $P < 0.001$; reference: Stage I+II), ELN $\leq 10$ (HR 1.75, 95% CI 1.37-1.23, $P < 0.001$; reference: $\geq 11$), LNR 0.49-1 (HR 7.70, 95% CI 5.38-11.01, $P < 0.001$; reference: 0-0.16), surgery of colectomy or greater (HR 3.47, 95% CI 1.95-6.17, $P < 0.001$; reference: Local resection) were predictors of poor CSS. The results are shown in Table 2.

**Survival analysis of ANET patients at different disease stages**

For the whole cohort, the median follow-up time was 31 months (range, 0-499 months), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 91.2%, 87.5%, and 81.7%, respectively. We calculated the 3-, 5-, and 10-year CSS rates of each stage, and the rate decreased as the stage increased as shown in Table 3. The 10-year CSS rates and most median CSS times were unknown. We also plotted survival curve for all patients (Figure 1, A) and curves based on the four stages (Figure 1, B).

**Impact of tumor size and surgery on the survival of ANET patients**

Tumor size $> 2$ cm is generally considered to be an important prognostic factor for patients with ANET, and it may also affect the choice of surgery. According to the North American Neuroendocrine Tumor Society (NANET) guidelines, $> 2$ cm is one of the criteria for right hemicolecotomy (RHC) for ANET patients[18]. The European Neuroendocrine Tumor Society (ENETS) guidelines also recommend aggressive
surgery for ANET patients with tumors > 2 cm due to the risk of recurrence and metastasis. In addition, tumor stratification is partly according to tumor size\(^{19}\). In the present study, we divided the tumor size and surgery into two categories. Univariate analysis suggested that there was a significant survival difference between tumor sizes and different surgeries by the log-rank test \((P < 0.001)\). The survival curves are shown in Figure 2. Patients with tumor \(\leq 2\) cm and who underwent local resection had better survival compared to the other categories.

To determine whether survival differences exist between surgical methods in different tumor size, we also conducted a survival analysis of two surgeries but divided the patients into two stratifications by tumor size. There were 225 patients for local resection and 1468 patients for colectomy or greater with tumor size \(\leq 2\) cm, while there were 21 patients for local resection and 584 patients for colectomy or greater with tumor size \(> 2\) cm (Figure 3, A). The log-rank test showed that there was no significant difference in both tumor size between the two surgeries \((P = 0.068,\ Figure 3, B; P = 0.523, Figure 3, C)\). The data analysis showed that when the tumor size was less than 2 cm, there was no survival benefit due to expansion surgery (Figure 3, B). Therefore, for ANET less than 2 cm, right hemicolecctomy should be carefully selected. According to our analysis results, when tumor was larger than 2 cm, the two different surgical methods did not show the expected survival difference (Figure 3, C), but only 21 patients with tumors larger than 2 cm chose local resection, which may have produced statistical bias.

**LN invasion associated with tumor size**

Small ANET are generally considered to be benign, and LN metastasis is rarely reported for tumor smaller than 2 cm\(^{18}\). There is a clearly increased risk of LN metastasis for ANET > 2 cm\(^{19}\), and the risk is up to 40\%\(^{20}\). In addition, a tumor diameter of 2 cm has been suggested to be associated with LN metastasis. To confirm of it in our cohort, 2202 patients were divided into two categories according to both tumor sizes and LN status (Table 4). There were a total of 1837 (85.1\%) node-negative patients and 329 (14.9\%) node-positive patients. For all 1613 patients with a tumor size \(\leq 2\) cm,
there were 1516 (94.0%) node-negative patients and only 97 (6.0%) node-positive patients. For all 589 patients with tumor size > 2 cm, there were 357 (60.6%) node-negative patients and 232 (39.4%) node-positive patients. The chi-squared test showed that there was a significant difference ($\chi^2 = 378.16, P < 0.001$). Patients with tumor size > 2 cm were more likely to be susceptible to LN metastasis (Figure 4).

**Impact of the number of ELN on survival**

We used X-tile software to identify the optimal number of ELN that generated the greatest survival difference. For the entire cohort, 11 LNs was the optimal number of ELN that generated the greatest survival difference ($\chi^2 = 20.303, P < 0.001$). The cutoff point was 7 LNs ($\chi^2 = 11.569, P = 0.001$) for node-negative patients and 18 LNs ($\chi^2 = 21.990, P < 0.001$) for node-positive patients. We further calculated the 3-, 5-, and 10-year CSS rates for patients based on LN status and different ELN (Table 5).

**Survival analysis of the optimal number of ELN for all patients**

For two categories divided by the ELN cutoff point of all patients, the median follow-up of patients with ≤ 10 ELN was 36 months (range, 0-306 months), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 83.2%, 76.1%, and 67.9%, respectively. For patients with ≥ 11 ELN, the median follow-up was 38 months (range, 0-347 months), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 90.3%, 85.5%, and 79.1%, respectively. Kaplan-Meier survival curve based on ELN cutoff points is plotted (Figure 5, A). Among all patients, patients with ≥ 11 ELN had a better CSS than patients with ELN ≤ 10 ($\chi^2 = 20.303, P < 0.001$). The results suggested that the number of LNs detected should be greater than or equal to 11 for a better survival and prognosis.

**Survival analysis of the optimal number of ELN for node-negative patients**

Considering node-negative patients, patients with ELN ≤ 6 had a median follow-up of 28 months (range, 0-306 months), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 94.9%, 86.5%, and 79.3%, respectively. For patients with ELN ≥ 7, the median follow-up was 43 months (range, 0-326 months), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 98.1%, 95.4%, and 90.1%,
respectively. We plotted survival curves based on ELN cutoff points of \( \leq 6 \) and \( \geq 7 \) for node-negative patients (Figure 5, B). Patients with \( \text{ELN} \geq 7 \) had a better CSS \((\chi^2 = 11.569, P < 0.001)\). The results suggested that the number of LNs detected in ANET patients with negative LNs is preferably greater than or equal to 7 for better survival.

**Survival analysis of the optimal number of ELN for node-positive patients**

For the node-positive patients, patients with \( \text{ELN} \leq 17 \) had a median follow-up of 31 months (range, 0-345 months), and the median CSS time was 60 months. The 3-, 5-, and 10-year CSS rates were 60.7%, 50.0%, and 40.6%, respectively. For patients with \( \geq \text{ELN} \) 18, the median follow-up was 35 months (range, 0-347 months), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 78.4%, 71.5%, and 61.4%, respectively. Kaplan-Meier survival curves based on ELN cutoff points for node-positive patients were plotted (Figure 5, C). Patients with \( \text{ELN} \geq 18 \) had a better CSS than patients with \( \text{ELN} \leq 17 \) \((\chi^2 = 24.464, P < 0.001)\). The results suggested that the number of LNs detected in ANET patients with positive LNs is preferably greater than or equal to 18 for better survival and prognosis.

**Survival analysis of the optimal LNR**

0.16 was the optimal cutoff point of LNR that generated the greatest survival difference for node-positive patients. The log-rank test showed that there were survival differences of 3 stratifications divided by two cutoff values of LNR \((\chi^2 = 160.406, P < 0.001)\). We calculated the 3-, 5-, and 10-year CSS rates for all node-positive patients by different LNR (Table 6). For all node-positive patients, the median follow-up was 33 months (range, 0-347 months), and the median CSS time was unknown. In addition, the 3-, 5-, and 10-year CSS rates for all node-positive patients were 67.3%, 58.4%, and 48.9%, respectively. For the three stratifications divided by the LNR cutoff points, the median follow-up of patients with LNR \( \leq 0.16 \) was 45 months (range, 0-347 months), and the median CSS time was unknown. The 3-, 5-, and 10-year CSS rates were 88.5%, 80.8%, and 68.9%, respectively. For patients with LNR between 0.17 and 0.48, the median follow-up was 32 months (range, 1-345 months), and the median CSS time was 46 months. The 3-, 5-, and 10-year CSS rates were 59.7%, 46.2%, and 37.4%, respectively.
For patients with a LNR $\geq 0.49$, the median follow-up was 16 months (range, 0-203 months), and the median CSS time was 18 months. The 3-, 5- and 10-year CSS rates were 24.7%, 17.7% and 14.2%, respectively.

LNR $\leq 0.16$ was associated with better CSS. Kaplan-Meier survival curves based on the LNR cutoff points were plotted (Figure 6). Survival differences existed between patients with LNR $\leq 0.16$ and patients with LNR between 0.17 and 0.48 ($\chi^2 = 48.243$, $P < 0.001$), $0.17 \leq$ LNR $\leq 0.48$ and LNR $\geq 0.49$ ($\chi^2 = 26.908$, $P < 0.001$) as well as between patients with LNR $\leq 0.16$ and patients with LNR $\geq 0.49$ ($\chi^2 = 168.485$, $P < 0.001$). Compared to patients with LNR $\geq 0.17$, patients with LNR $\leq 0.16$ were more likely to have better survival. Thus, LNR $\leq 0.16$ may be the critical point for determining the better survival prognosis of ANET patients.

**DISCUSSION**

ANET are mostly discovered coincidentally during appendectomy and usually have a benign clinical course. As the majority of all appendiceal neoplasms, ANET are rare for appendiceal neoplasms\textsuperscript{21}. These tumors are generally confirmed by pathological examination in appendectomy specimens\textsuperscript{22}. In ENETS guidelines, tumor size (including T class), localization within the appendix, extent of invasion into the mesoappendix, and vascular invasion are the main prognostic features. Tumor size, meso-appendiceal invasion, tumor grade, tumor location, and angio or lymphatic invasion are considered as risk factors that may be associated with disease course and therapy methods\textsuperscript{20}. Under some circumstances, RHC should be considered as an additional operation after appendectomy in 3 months\textsuperscript{19, 23, 24}. NANET and ENETS guidelines show that tumor size is closely related to the survival, and the prognosis of patients with tumors $\geq 2$ cm is worse. Moreover, deep invasion, regional metastasis, and LN metastasis are also related to tumor size\textsuperscript{18}. Abdelaal et al.\textsuperscript{12} reviewed 32 appendectomy specimens that histologically confirmed NET and indicated that appendectomy is an adequate surgical method patients with tumors smaller than 2 cm with negative pathological margins. Bamboat and Berger\textsuperscript{25} reported on 5 patients with
tumors greater than 2 cm and 4 of the patients were treated by secondary RHC following appendectomy, and they were all alive with a mean follow-up of 10 years (range, 1-15 years). Moertel et al. reported that 150 patients with ANET, LN metastasis was observed in 7 (30.43%) of 23 patients with tumors ≥2 cm, while no LN metastasis was observed in 123 patients with tumors <2 cm. Mullen reported that LN metastases were present in 44 of 89 patients (49%), including 4 of 27 patients (15%) with tumors ≤1.0 cm, 16 of 34 patients (47%) with tumors between 1.0 cm and 2.0 cm, and 24 of 28 patients (86%) with tumors > 2.0 cm, and they concluded that increasing tumor size predicts LN involvement.

Tumor > 2 cm is the most accepted risk factor, but it still remains controversial. According to published data, the cutoff value of tumor size related to LN involvement is 1.55 cm. Rault-Petit suggested that 1.95 cm is the optimal cutoff value of tumor size to predict LN status of ANET. Sarshekeh et al. suggested that 1 cm is a more appropriate cutoff than 2 cm for predicting LN metastasis. Kleiman et al. performed a retrospective study of 79 patients and noted that small-vessel invasion of tumor < 2 cm has similar metastatic potential as ≥ 2 cm. Except, histology is also a significant LN metastasis predictor. Pawal suggested that the differentiation grade may be associated with LN metastasis because all G2 and G3 patients have regional LN metastasis. Brighi et al. reported that G2 and lymphovascular infiltration are related to LN involvement other than tumor size >1.55 cm. Tang suggested that patient with tumors ≥2 cm but with subserosa or mesoappendix invasion, lymphovascular invasion, or increased mitotic activity (> 2 mitoses per 50 high-power fields) are at risk for LN or distant metastasis in some cases. For tumor size and LN metastasis in the present study, patients with tumors > 2 cm had a LN metastasis rate of 39.4% compared to the rate of 6.0% in patients with tumors ≤ 2 cm. The χ² showed that there was a statistical significance, indicating that tumor size > 2 cm is a factor associated with LN metastasis. At present, there is no factor or rule that completely and accurately predicts LN metastasis. Until additional evidence becomes available, our data analysis combined
with the results of most research suggest that tumor larger than 2 cm is still considered to be an important risk factor for LN metastasis.

In terms of treatment, ENETS guidelines recommended that tumors diameter > 2 cm should be treated by RHC\textsuperscript{20}. However, a substantial number of patients may not received appropriate surgical resection despite the current treatment recommendations. A population-based retrospective study has suggested that 28\% ANET patients with tumors > 2 cm do not undergo RHC, whereas 3.47\% with tumors > 2 cm did not undergo RHC in the present study\textsuperscript{34}. For patients with tumors > 2 cm, 96.53\% of them underwent colectomy or greater surgery, and 86.71\% of patients with tumors ≤ 2 cm underwent colectomy or greater surgery. Thus, these findings suggested that it is not appropriate to perform colectomy or greater surgery only on the basis of tumor size. Grozinsky-Glasberg et al.\textsuperscript{35} suggested that when using the latest ENETS criteria for RHC, the risk of residual disease is high in patients with a primary tumor size of 1-2 cm, and residual disease may be missed in 18\% of ANET patients because pathological factors are ignored. Univariate survival analysis showed that there was a significant difference between patients with tumors > 2 cm and ≤ 2 cm in the present study, but there was no survival difference between the two surgeries stratified according to tumor size. Sarshekeh\textsuperscript{16} suggested that differentiation grade and LN involvement are associated with prognosis irrespective of surgery type. Groth et al.\textsuperscript{31} reported that there is no significant difference in the survival rate between hemicolecystomy and appendectomy. Similar results were obtained in our study for patients with tumors ≤ 2 cm and > 2 cm. Colectomy or greater resection did not statistically improve the outcome, but there was a better survival rate for patients with tumors ≤ 2 cm and patients who underwent local resection. Importantly, 74.78\% of patients with tumors ≤ 2 cm underwent colectomy or greater resection, indicating that some patients do not undergo proper surgical treatment and that colectomy or greater resection should be strictly applied, especially for those patients with tumors ≤ 2 cm. Volante\textsuperscript{36} suggested that RHC recommended by the NANET/ENETS guidelines should be followed even though there is no survival difference. Our data analysis showed that when the tumor
size was less than 2 cm, there was no survival benefit due to expansion surgery. Therefore, for ANET less than 2 cm, right hemicolecction should be carefully selected. According to our analysis results, when the tumor was larger than 2 cm, the two different surgical methods did not show the expected survival difference. However, only 21 patients with tumors larger than 2 cm chose local resection, which may have produced statistical bias. Thus, our findings suggested that it is inappropriate to perform colectomy or larger surgery based only on the size of the tumor. Therefore, we inferred that the survival benefits of the different surgical methods are not due to the choice of surgical methods but instead are due the difference in the size of the tumor. Because most patients with tumors larger than 2 cm tend to choose colectomy, the prognosis of such patients is inherently worse than those with tumors smaller than 2 cm. Therefore, the prognosis of patients who choose colectomy is worse than local resection, which is probably not caused by the choice of surgical method but by the size and stage of the tumor itself. Combined with the recommendations of guidelines, most studies and our data analysis suggest that patients with tumors larger than 2 cm are more inclined to choose colon resection and that it is unnecessary to blindly expand the scope of surgical resection for patients with tumors ≤ 2 cm.

ANET are often thought to have good outcomes, and the 10-year survival rate has been reported to reach up to 95%. A previous study has reviewed 83 ANET patients diagnosed during 1976-1987 indicated that 53 of 56 (94.6%) were alive[13]. A retrospective study has revealed that the 5-year survival rate of 17 patients with ANET was as high as 100%. A recent retrospective study with a larger sample reported a low CSS rate. In the present study, the survival data indicated 10-year, 5-year, and 3-year CSS rates of 81.7%, 87.5%, and 91.2%, respectively. Moreover, our analysis also calculated survival rates based on disease stage to obtain additional details for the 3- and 5-year CSS rates of patients with disease stages I-IV. The highest 3-year rate was 99.7% for stage I, and the lowest 5-year rate was 25.1% for stage IV.

LN metastasis is often thought to be associated with poor outcomes. Node-positive patients have a significantly worse survival rate even though patients who have
undergone hemicolecotomy also have 12 ELN\textsuperscript{[31]}. Similar results have been confirmed in another study, which indicated that survival is markedly worse despite RHC being conducted in mixed adenoneuroendocrine carcinoma patients with LN metastasis\textsuperscript{[16]}. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology recommend that 12 LNs should be evaluated at least in colorectal cancer to allow patients to be pathologically assessed accurately and optimally staged based on adequate resected LNs\textsuperscript{[37]}. However, to date, few studies have focused on the impact of the optimal number of ELN on survival for ANET. We divided all patients into two groups according to the number of ELN, and the most significant survival difference existed between patients with ELN \leq 10 and patients with ELN \geq 11. For a certain lymph status, node-negative patients with ELN \geq 7 had the most significant survival difference and \geq 18 for node-positive patients. The optimal number of ELN may be transformed into LNs and should be surgically retrieved after further confirmation in the future, especially for patients suspiciously diagnosed as ANET preoperative. Except for tumor size, more factors should be taken into account and more detail criterion should be regulated to chose a surgery type for ANET patients.

The LN status of most malignancies has long been categorized according to the number of metastatic LNs in the AJCC TNM system\textsuperscript{[38]}. However, the number of LNs to be examined often has an influence on the number of metastatic LNs pathologically confirmed. Moreover, the LNR is considered a better prognostic determinant than the number-based LN staging system for colon cancer\textsuperscript{[39]}. The LNR takes both ELN and positive LN into account. There is no unified criterion has been established for LNR stratification of ANET. The use of quartiles may be the most prevalent method and has been applied in diverse studies. With X-tile software, we adopted 0.16 and 0.48 as cutoff points to divide patients into 3 groups. The 3-, 5-, and 10-year CSS rates significantly increased with a lower ratio (\leq 0.16). To some extent, the present study agreed with the study by Vaccaro et al.\textsuperscript{[40]}, who found that colon cancer patients with a LNR \textless{} 0.25 have better survival. Lee et al.\textsuperscript{[41]} also suggested that a LNR \textless{} 0.11 is associated with significantly better 5-year disease-free survival. Shinto et al.\textsuperscript{[42]} mentioned that patient
with a low LNR have a higher 5-year CSS rate; The LNR cutoff is 0.18 for all colon
cancer patients and 0.16 and 0.22 for right and left colon cancer patients, respectively.
The LNR cutoff of ANET in the present study was similar to the values proposed by
other studies. For node-positive patients, LNR ≤ 0.16 increased the 3-, 5-, and 10-year
CSS rates from 67.3%, 58.4%, and 48.9% to 88.5%, 80.8%, and 68.9%, respectively. Our
analysis results suggested that higher LNR result in worse survival prognosis. Thus,
LNR ≤ 0.16 may be the critical point for determining a better survival of ANET patients.

**CONCLUSION**

In summary, the univariate survival analysis conducted in the present study showed
that most factors are related to survival. Patients with tumor size > 2 cm are more likely
to develop LN invasion and metastasis with a worse prognosis. Regarding the choice of
surgical methods, for patients with tumors ≤ 2 cm, there is no need to blindly expand
the scope of surgical resection. Higher positive rate of LN metastasis in patients with
ANETs result in worse survival prognosis. The optimal number of ELN for all patients,
node-negative patients, and node-positive patients are 11, 7, and 18, respectively. LNR ≤
0.16 may be the key point for determining a better survival prognosis of patients with
ANETs.
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