Endoscopic Resection Versus Surgical Resection for Gastric Neuroendocrine Neoplasms Without Distant Metastasis

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Abstract

Background: Resection is the main method for treating gastric neuroendocrine neoplasms (g-NENs). However, the threshold for tumor size needs to be removed, and the prognostic difference between the endoscopic and surgical resection groups remains unclear. Methods: In this study, 929 g-NENs patients without distant metastasis were collected and analyzed (857 patients from the SEER database, 72 patients from Wuhan Union Hospital or the First Affiliated Hospital of Shihezi University). Results: Overall, for g-NENs without distant metastasis, the resected group had a better prognosis than the unresected group (p =0.0019). For tumor >2cm, the resection group had a better prognosis than the unresected group (p =0.0002), but there was no significant difference in survival between the endoscopic and surgical resection group (p >0.05). For tumor <1cm or 1-2cm, there was no significant difference in survival between the resected group and the unresected group, and there was no significant difference in survival between the endoscopic resection group and the surgical resection group (p >0.05). Furthermore, for g-NENs confined to in-situ and T1, or with well-differentiated morphology or w/wo lymph node metastasis without distant metastasis, there was no significant difference in prognosis between the endoscopic resection group and the surgical resection group (p >0.05). Conclusions: Resection can significantly improve the prognosis of g-NENs patients without distant metastasis, and 2cm can be used as a resection threshold. For g-NENs within the size of endoscopic resection, which localized in situ and T1, or with well-differentiated morphology, or w/wo lymph node metastasis without distant metastasis, endoscopic resection is feasible.

Background

Neuroendocrine neoplasms (NENs) are thought to originate from neuroendocrine cells and peptidergic neurons throughout the body and are characterized by their rarity and inertia. But the actual incidence of NENs is steadily rising, with a 6.4-fold increase from 1973 (1.09 per 100,000) to 2012 (6.98 per 100,000), according to the latest epidemiological data reported by the Surveillance, Epidemiology, and End Results (SEER) program. Thereinto, the rise in incidence was highest in the stomach, which was 15-fold [1].

Main treatment options for gastric NENs (g-NENs) are resection (endoscopy or surgery), pharmacotherapy or observation, as suggested both by National Comprehensive Cancer Network (NCCN) (2015) and European Neuroendocrine Tumor Society (ENETS) (2016) guidelines. Although both the NCCN and ENETS guidelines consider tumor size as a basis for g-NENs treatment selection, there is controversy over the size of the tumor that needs to be removed. The NCCN guidelines recommend endoscopic resection (if possible) or surgical resection for g-NENs patients with the tumor larger than 2cm but without distant metastasis. However, ENETS recommends resection when the tumor is larger than 1 cm for g-NENs patients without distant metastasis [2, 3]. Therefore, it is of great significance to define the tumor size threshold for g-NENs resection.

The aim of this study was to determine the tumor size threshold for resection of g-NENs without distant metastasis and to identify the prognostic factors for them. Therefore, we retrospectively reviewed and

analyzed the clinical data of g-NENs patients without distant metastasis from the SEER program from 1975 to 2016, Wuhan Union Hospital and the First Affiliated Hospital of Shihezi University from 2009 to 2019.

Methods

Patients and data collection

SEER dataset was collected from the SEER Program (www.seer.cancer.gov) SEER*Stat Database, including 18 regions between the inception of the SEER program in 1975 until December 31, 2016, based on the November 2018 submission. The data used in this study was obtained from SEER program by signing the SEER Research data Agreement form, a public open database. Third Edition (ICD-O-3) histology codes were used to identify g-NENs of the SEER database (8013, large cell neuroendocrine carcinoma; 8153, gastrinoma; 8240, carcinoid tumor; 8241, enterochromaffin cell carcinoid; 8244, mixed adenoneuroendocrine carcinoma; 8245, adenocarcinoid tumor; 8246, neuroendocrine carcinoma; and 8249, atypical carcinoid tumor). A total of 857 patients diagnosed with g-NENs without distant metastasis were collected using SEER registers from 1975 to 2016. The detailed information about these patients was collected , including age, sex, race, differentiation, tumor site, TNM stage based on the 7th edition of the AJCC staging system, tumor size, treatment, survival months, and end status.

The clinical dataset included data from 72 patients who diagnosed with g-NENs but without distant metastasis at Wuhan Union Hospital or the First Affiliated Hospital of Shihezi University from 2009 to 2019.

Statistical analysis

Data were analyzed with SPSS software v26.0 (IBM, USA) or GraphPad Prism v8.0c. Clinical and pathological features were expressed as median and range, absolute value or fractions. Differences in categorical variables were compared with chi-square test or Fisher's exact test. A Mann-Whitney U-test was used to compare the median tumor size between groups. We used the Kaplan-Meier (K-M) method for survival analysis, log-rank tests were used for comparing differences between groups. Cox proportional hazards regression analysis was used to assess prognostic factors for survival. $P<0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 857 patients diagnosed with g-NENs without distant metastasis from SEER database were analyzed in this study. The median age at diagnosis was 60 years (range: 17-99 years). There were 350 (40.8%) males and 507 (59.2%) females (female-male ratio of 1.45). The distribution of g-NENs from SEER dataset was gastric body (29.4%, 252/857), cardia and gastric fundus (18.1%, 155/857), antrum

and pylorus (10.6%, 91/857), and unspecified parts of the stomach (23.3%, 200/857). In terms of tumor size, 490/587 patients (57.2%) were less than 1cm, 203/587 patients (23.7%) were larger than 2cm and 164/587 patients (19.1%) were between 1 to 2 cm. Most of the patients were well-differentiated (88.2%). Lymph node metastasis were found in 138 (16.1%) of all patients.

A total of 72 patients from Wuhan Union Hospital and the First Affiliated Hospital of Shihezi University from 2009 to 2019 were collected and assigned as the clinical dataset (clinical characteristics were presented in **Table 1**). The median age at the diagnosis was 59 years (range: 32-86). There were 23 (31.9%) females and 49 males (68.1%). Cardia and gastric fundus (40.3%, 29/72) was the most common tumor site, followed by gastric body (29.2%, 21/72), and antrum and pylorus (15/72, 20.8%). In terms of tumor size, 16/72 patients (22.2%) were less than 1cm, 45/72 patients (62.5%) were larger than 2 cm and 11/72 patients (15.3%) were between 1 to 2 cm. Lymph node metastasis occurred in 32 (44.4%) patients.

Endoscopic resection vs. surgical resection for g-NENs without distant metastasis

Tumor size

A total of 743 (86.7%) of patients in the SEER dataset and 66 (91.7%) of patients in the clinical dataset received resection treatment. Overall, K-M analysis showed that patients who underwent resection had a better prognosis than those who did not, both in the SEER dataset (p=0.0019, **Figure 1A)** and in the clinical dataset (p=0.0004, **Figure 1E**). Next, we compared the prognosis between resection group and unresected group based on tumor size. For tumors larger than 2 cm, the resection group had a better prognosis than unresected group both in the SEER dataset (p=0.0002, **Figure 1B)** and in the clinical dataset (p=0.0011, **Figure 1F**). However, for tumors smaller than 1 cm and those between 1 and 2 cm in size, there was no significant difference in survival between resection group and unresected group (p>0.05, **Figure 1C, D and G**).

Moreover, we further analyzed and compared the prognosis of patients with tumors larger than 2 cm with different resection methods. In the SEER dataset, 178 patients with tumors larger than 2 cm underwent resection, of which 31/178 (17.4%) underwent endoscopic resection and 147/178 (82.6%) underwent surgical resection. For tumors larger than 2 cm, K-M analysis showed that there was no significant difference in survival between endoscopic resection group and surgical resection group (p=0.0588, **Figure 2A**). For tumors larger than 2cm that underwent resection, the median tumor size was 2.5 cm in endoscopic resection group and 4.0 cm in surgical resection group (p<0.001, **Table 2**). For tumors smaller than 1cm or those between 1 and 2 cm in size, there was also no significant difference in survival between endoscopic resection group and surgical resection group (p>0.05, **Figure 2B and C)**.

Depth of tumor invasion

In this study, the SEER dataset was analyzed to investigate the relationship between the depth of tumor invasion and the outcome of different resection methods. In the resected group, in-situ tumors accounted for 5.1% (38/743), T1 50.9% (378/743), T2 28.1% (209/743), T3 10.9% (81/743) and T4 5.0% (37/743).

For tumors larger than 2cm confined to in-situ and T1, the prognosis was similar between the endoscopic resection group and the surgical resection group (p=0.2457, **Figure 3A**). For tumors smaller than 1 cm or between 1 and 2 cm confined to in-situ and T1, there was also no significant difference between endoscopic resection group and surgical resection group (p>0.05, **Figure 3B and C**). Therefore, we conclude that endoscopic resection and surgical resection are feasible for g-NENs limited to in-situ and T1, whether smaller than 1cm, between 1 and 2 cm or larger than 2 cm.

Lymph node metastasis

The relationship between lymph node metastasis and the prognosis of different resection methods was also explored. In g-NENs patients without lymph node metastasis (618/743, 83.2%), there was no difference in prognosis between the endoscopic resection group and the surgical resection group, whether the tumor was smaller than 1 cm, between 1 and 2 cm or larger than 2 cm. (p>0.05, **Figure 4A-C**). More importantly, in patients with lymph node metastasis (125/743, 16.8%), no difference in prognosis was found between the endoscopic resection group and the surgical resection group, whether smaller than 1 cm, between 1 and 2 cm or larger than 2 cm (p>0.05, **Figure 4D-F**).

Differentiation

Furthermore, the prognosis difference between different resection methods in well-differentiated g-NENs was compared. The results showed that the prognosis of the endoscopic resection group was similar to that of the surgical resection group, whether the tumor was smaller than 1 cm, larger than 2 cm, or between 1 and 2 cm in size (p>0.05, **Figure 5A-C)**. Due to the limited number of patients with poorly-differentiated morphology undergoing endoscopic resection, we were unable to compare the difference in survival between the endoscopic resection group and surgical resection group based on tumor size.

Prognostic analysis

To further investigate the prognostic factors related to the prognosis of g-NENs without distant metastasis, we conducted univariate analysis, including age, sex, race, differentiation, tumor site, tumor size, TNM stage, T stage, N stage, whether or not resection treatment was given and resection methods. Results of univariate and multivariate Cox regression analysis for survival were summarized in **Table 3**. The Cox regression analysis showed that age≥55 (p=0.002), poorly-differentiation (p=0.001), tumor larger than 2cm (p=0.020) and not receiving resection treatment (p=0.000114) were negative prognostic factors for survival of g-NENs patients without distant metastasis.

Discussion

This retrospective study was based on SEER data from 1975 to 2016 and combined with clinical data from Wuhan Union Hospital and the First Affiliated Hospital of Shihezi University from 2009 to 2019 to study the clinicopathological features, treatment and prognostic factors of g-NENs without distant metastasis.

Gastroenteropancreatic NENs (GEP-NENs) are highly heterogeneous [2, 4-8], accounting for more than half of all NENs (61%) [9]. Among them, the gastric is one of the most common parts of GEP-NENs [10-13], and the proportion of g-NENs in GEP-NENs varies, ranging from 5.6% to 8.7% [9, 14-17]. GEP-NENs are typical inert tumors with different aggressiveness depending on the primary site. Small intestinal NENs are more likely to develop malignant tumors, while g-NENs are less likely to metastasize, so the prognosis is better [6]. The incidence of g-NENs has risen steadily over the past 40 years, probably due to the increased use of endoscopy and imaging techniques, as well as the use of standardized staging and pathology guidelines [1, 9, 18, 19]. Recent epidemiologic evidence suggests that the incidence of g-NENs is between 0.3% to 1.8% of all gastric tumors [20, 21]. Studies from national histopathology or endoscopy database have shown that the prevalence of g-NENs ranks in the top 5 among the gastric polypoid lesions, and about 3.3% of gastric polypoid lesions are neuroendocrine tumors (NETs) [22, 23]. Therefore, it is important to enhance the understanding of g-NENs.

There are many treatment options for g-NENs patients, such as resection, somatostatin analogues, interferon, chemotherapy, etc.[24], but resection is still the first choice for most g-NENs patients without distant metastasis [3, 10, 11, 25]. However, in different studies and guidelines, the criteria for the size of the tumor to be removed vary. Most studies recommend only surveillance for lesions smaller than 1 cm and limited to the mucosa and submucosa [6, 7]. Ravizza et al. followed 11 untreated patients with type I g-NENs (TIGC) ≤1 cm for an average of 54 months, and found no change in lesion diameter and no lymph node or distant metastasis during the follow-up[26]. But some investigators advocate removing all visible lesions [27-30]. The ENETS guidelines (2016) recommend 1 cm as the threshold for resection in patients without distant metastasis [2], while in the NCCN guidelines (2015) recommend 2 cm as the threshold for resection [3].

In our study, we found that, on the whole, for patients with g-NENs, those who underwent resection had a better prognosis than those who did not. When we further compared the prognosis based on the tumor size, we found that there was a significant difference in survival time between resected and unresected patients with g-NENs larger than 2cm, but there was no survival benefit for patients with g-NENs less than 2cm. The results from both the clinical dataset and the SEER dataset support the NCCN guidelines (2015).

For g-NENs, endoscopic resection and surgical resection are both feasible, but the difference in prognosis between these two methods is still unclear. Therefore, we further analyzed the difference in prognosis between the endoscopic resection group and the surgical resection group in patients undergoing resection. Results from the SEER dataset showed no significant difference in survival between the endoscopic and surgical resection groups, regardless of tumor size. Tumor size, invasion depth, lymph node metastasis and differentiation are all factors that should be considered for endoscopic treatment of gastric tumors [28, 31]. Therefore, we also explored the relationship between the outcome of different resection methods and the depth of tumor invasion, lymph node metastasis or differentiation. We found that for g-NENs confined to in-situ and T1, or tumors with well-differentiated morphology or w/wo lymph node metastasis, the prognosis of the endoscopic resection group was similar to that of the surgical

resection group. According to the Japanese guidelines for the treatment of gastric cancer (2018), differentiated early gastric cancer with a depth of T1 and a diameter ≤3 cm indicate endoscopic therapy [32]. Angelena et al. found no significant difference in recurrence-free survival between the group undergoing local resection (endoscopic and wedge resection) and the group undergoing formal gastrectomy [33]. For patients with g-NENs, the duration of surgical treatment is long, the incidence of complications is high and the rate of readmission is high, while endoscopic resection can provide a similar survival outcome, and the incidence of complications and readmission is low and the operative time is short [27, 33-35]. Therefore, we conclude that for g-NENs located in-situ and T1, or with well-differentiated morphology, or w/wo lymph node metastasis, but no distant metastasis, endoscopic resection is feasible within the size of endoscopic resection.

There are several limitations to this study. First, information about the functional status, Ki-67 index and clinical type of g-NENs in SEER database are unavailable due to retrospective design. Second, the median survival time of this study was not obtained due to the short follow-up time and indolent disease course, which was the inherent characteristic of g-NENs. Third, this study is limited by a relatively small sample size in the clinical dataset despite the clinical data from 2 tertiary academic centers, which reflected the rarity of g-NENs.

In summary, we confirmed that resection treatment can significantly improve the prognosis of g-NENs patients without distant metastasis. Age≥55, poorly differentiation, tumor >2 cm and not receiving resection treatment were all independent negative prognostic factors for g-NENs without distant metastasis. Based on data analysis both in SEER dataset and clinical dataset, we proposed 2 cm as an optimal threshold to perform resection treatment. For g-NENs located in-situ and T1, or with well-differentiated morphology, or w/wo lymph node metastasis, but no distant metastasis, endoscopic resection is feasible within the size of endoscopic resection.

Abbreviations

g-NENs: Gastric neuroendocrine neoplasms; NENs: Neuroendocrine neoplasms; SEER: Surveillance, Epidemiology, and End Results; NCCN: National Comprehensive Cancer Network; ENETS: European Neuroendocrine Tumor Society; GEP-NENs: Gastroenteropancreatic NENs; NETs: Neuroendocrine tumors; TIGC: Type I g-NENs; HR: hazard ratio; 95% CI: 95% confidence interval.

Declarations

Acknowledgements

Not applicable.

Authors'contributions

* Huiying Shi and Hailing Yao contributed equally to this work.

Rong Lin designed and supervised the study and data analysis. Huiying Shi and Hailing Yao performed most of the data collection, analysis and wrote the manuscript; Shuxin Tian and Chen Jiang supported the data collection and analysis; Qin Zhang provided guidance in histopathological analysis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Ethical approval and consent to partcipate

The study was a retrospective study and approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (IORG No: IORG0003571), and performed in accordance with the Declaration of Helsinki.

Competing Interest

All authors declare no conflicts of interest.

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Figures

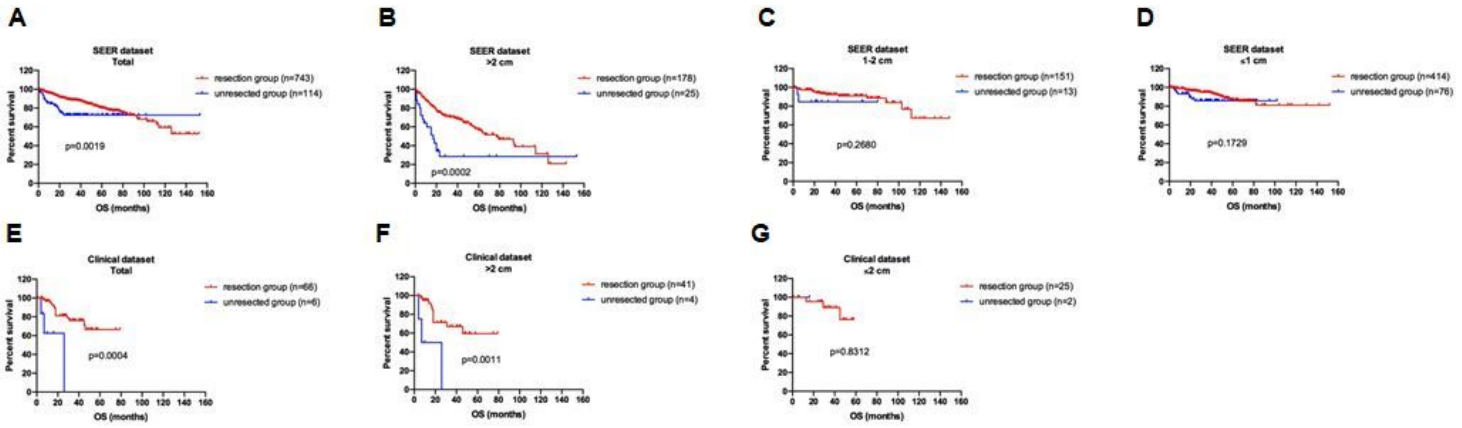

Figure 1

Kaplan-Meier curves for g-NENs patients without distant metastasis based on whether resection is performed. (A-D) Survival in the SEER dataset, A) Total, B) >2 cm, C) 1-2 cm, D) ≤1 cm; (E-G) Survival in the clinical dataset, E)Total, F) >2 cm, G) ≤2 cm.

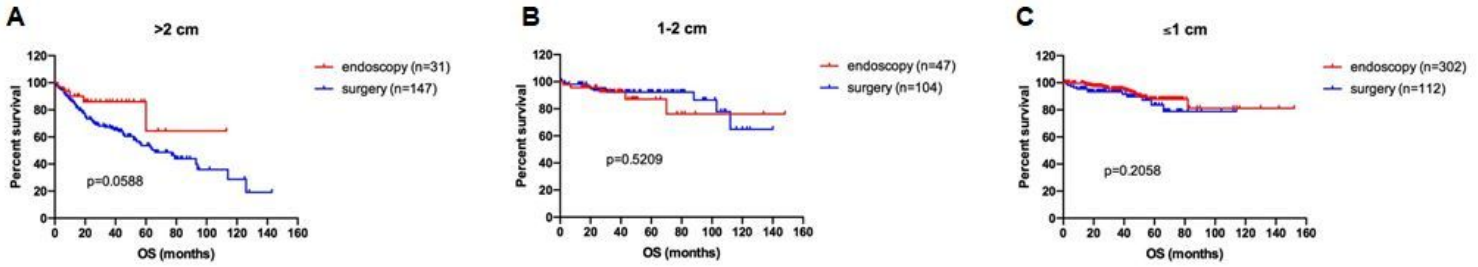

Figure 2

Kaplan-Meier curves for g-NENs patients without distant metastasis according to resection method and tumor size. (A) >2 cm, (B) 1-2 cm, (C) ≤1 cm.

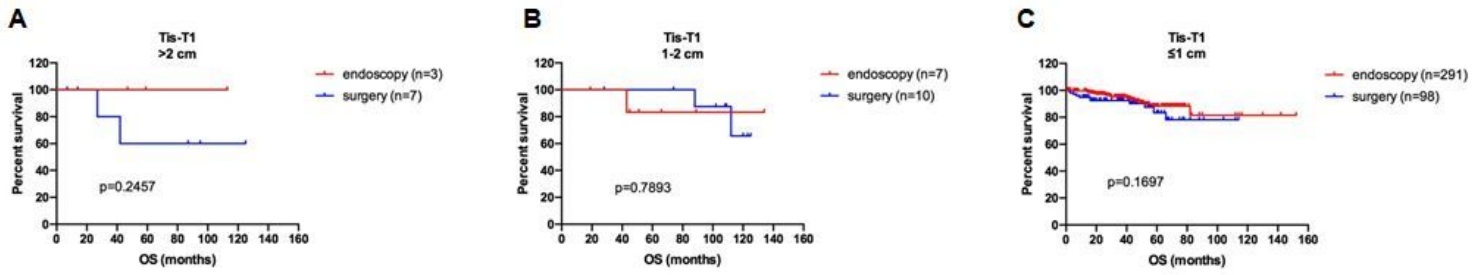

Figure 3

Kaplan-Meier curves for g-NENs patients limited to in-situ and T1 but without distant metastasis according to resection method and tumor size. (A) >2 cm, (B) 1-2 cm, (C) ≤1 cm.

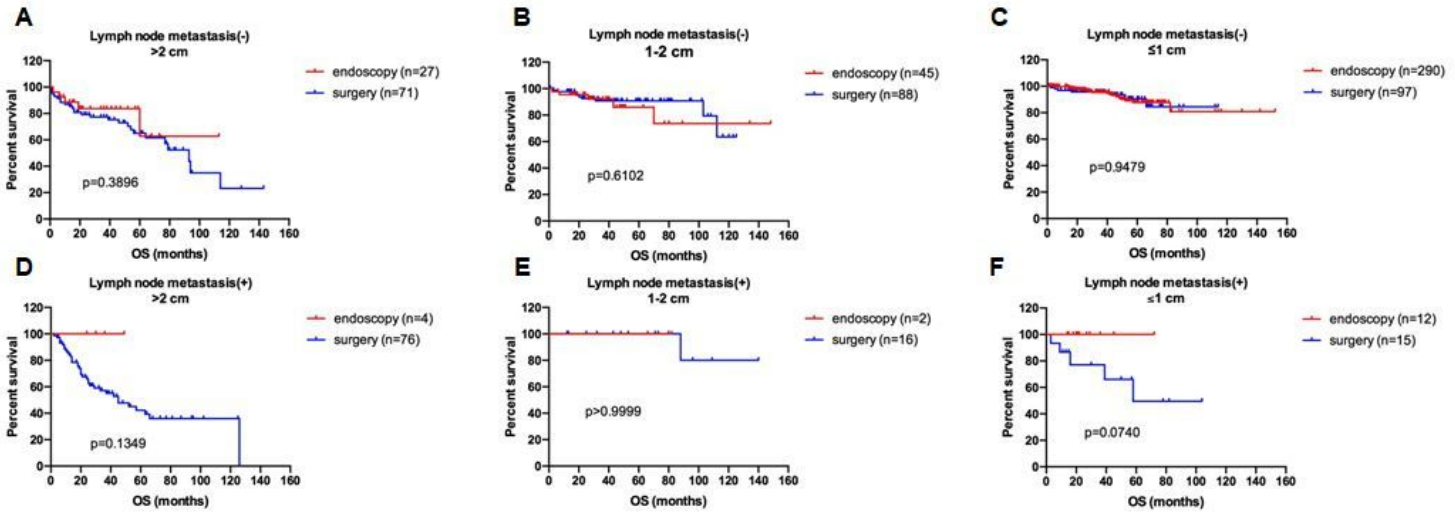

Figure 4

Kaplan-Meier curves for g-NENs patients without distant metastasis according to resection method, tumor size and lymph node metastasis. (A-C) Survival in the lymph node (-) tumor, A) >2 cm, B) 1-2 cm, C) ≤1 cm; (D-F) Survival in the lymph node (+) tumor, D) >2 cm, E) 1-2 cm, F) ≤1 cm.

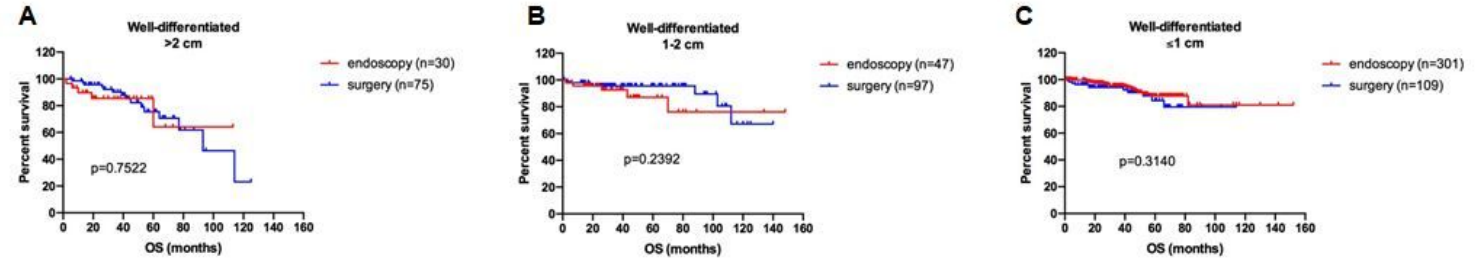

Figure 5

Kaplan-Meier curves for g-NENs patients with well-differentiated morphology but without distant metastasis according to resection method and tumor size. (A) >2 cm, (B) 1-2 cm, (C) ≤1 cm