Original Article

Textbook Outcome as a measure of surgical quality assessment and prognosis in gastric neuroendocrine carcinoma: A large multicenter sample analysis

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Abstract

Objective: Quality assurance is crucial for oncological surgical treatment assessment. For rare diseases, single-quality indicators are not enough. We aim to develop a comprehensive and reproducible measurement, called the "Textbook Outcome" (TO), to assess the quality of surgical treatment and prognosis of gastric neuroendocrine carcinoma (G-NEC) patients.

Methods: Data from patients with primary diagnosed G-NEC included in 24 high-volume Chinese hospitals from October 2005 to September 2018 were analyzed. TO included receiving a curative resection, ≥15 lymph nodes examined, no severe postoperative complications, hospital stay ≤21 d, and no hospital readmission ≤30 d after discharge. Hospital variation in TO was analyzed using a case mix-adjusted funnel plot. Prognostic factors of survival and risk factors for non-Textbook Outcome (non-TO) were analyzed using Cox and logistic models, respectively.

Results: TO was achieved in 56.6% of 860 G-NEC patients. TO patients had better overall survival (OS), disease-free survival (DFS), and recurrence-free survival (RFS) than non-TO patients (P<0.05). Moreover, TO patients accounted for 60.3% of patients without recurrence. Multivariate Cox analysis revealed non-TO as an independent risk factor for OS, DFS, and RFS of G-NEC patients (P<0.05). Increasing TO rates were associated with improved OS for G-NEC patients, but not hospital volume. Multivariate logistic regression revealed that non-lower tumors, open surgery, and >200 mL blood loss were independent risk factors for non-TO patients (P<0.05).

Conclusions: TO is strongly associated with multicenter surgical quality and prognosis for G-NEC patients. Factors predicting non-TO are identified, which may help guide strategies to optimize G-NEC outcomes.

Keywords: Textbook Outcome; gastric neuroendocrine carcinoma; surgical quality; prognosis; risk factor

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Introduction

Gastric cancer (GC) is the second most common malignant tumor and the third cause of cancer-related deaths (1,2). However, gastric neuroendocrine carcinoma (G-NEC), a particular type of GC, has very rare morbidity, despite having a common origin with GC. In recent years, as surgical knowledge of G-NEC has advanced, diagnosis and treatment for this type of tumor has also become increasingly standardized. Nevertheless, a G-NEC prognosis still leads to more adverse outcomes than common GC (3-5). Currently, many researchers are exploring clinical factors and novel therapies related to G-NEC to improve prognosis. In addition to the tumor's effect itself, it is being gradually recognized that quality control of perioperative health services also has a profound effect on the patient's survival. For more common types of tumors, such as GC, some major clinical centers may deal with numerous cases in a short time (6). Currently, the largest number of GC cases reported was 10,000 in a single hospital (7). Consequently, even for a single center, seeking appropriate medical quality control targets can be easily achieved by gradually accumulating clinical experience and sequentially increasing the recognition of pathological features. Surgeons often use a single stable parameter to complete the quality control of surgery amongst a large amount of accumulated treatment data. However, similar to other rare tumors, G-NEC cases often occur with a scatter-point distribution in time and place, making long-term follow-ups difficult. Simultaneously, international reports are generally small sample studies (8,9), and it is difficult to summarize effective, reproducible quality control metrics with a single-center study. Furthermore, an excessive focus on single parameters may disregard the multidimensionality of the complex surgical therapy of rare diseases. Therefore, it is necessary to carry out multicenter studies to integrate the available scattered data and find an ideal composite index for surgical quality assessment. In 2013, Kolfschoten *et al*. (10) first proposed the composite index of "Textbook Outcome (TO)", whose value has been gradually recognized in the assessment of care quality and prognosis of common tumors. Given its combination of available short-term data, including radical resection, number of lymph node dissections, postoperative complications, postoperative hospital stay, and post-operative readmission, TO is technically more suitable as an index of surgical quality control for rare diseases. However, there is still no literature reporting on the potential value of TO for the treatment of G-NEC patients with gastrectomy, and their long-term prognostic outcome. Hence, this study aimed to collect the clinical data of G-NEC patients from 24 Chinese hospitals, to carry out the first multicenter study revealing the value of TO for this rare disease. We developed a comprehensive and reliable indicator for those who received radical G-NEC surgery and analyzed the potential of TO in assessing surgical quality and prognosis. We hope to provide a tool to evaluate surgical quality systematically, improve the standards of surgical treatment, and guide clinical practice about the best care resources.

Materials and methods

Study design and cohort

We retrospectively analyzed the data of 860 G-NEC patients with complete information between October 2005 and September 2018, from the Study Group for Gastric Neuroendocrine Tumors (SGGNET) (11,12). SGGNET included 24 high-volume Chinese hospitals. The following exclusion criteria were applied: 1) missing survival data; 2) Mx and preoperative or postoperative M1 diagnosis; or 3) patients without surgery; After these evaluations, 860 G-NEC patients were considered. The selection scheme is provided in *Supplementary Figure S1*.

This study was conducted with the approval of the Institutional Review Boards of all participating hospitals. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients for inclusion in the study.

Definitions

In this study, TO refers to a combination of five quality

metrics related to oncologic resection, postoperative course, and discharge of patients undergoing G-NEC surgery. These include: a curative resection; ≥15 lymph nodes (LNs) examined; no severe postoperative complications; a hospital stay ≤21 d; and no hospital readmission ≤30 d after discharge. When all parameters were met, TO was achieved. There is no generally acknowledged definition of TO for G-NEC. With respect to the previously published literature (10,13-20), we have modified the definition of TO to conform to this analysis and the data available from SGGNET. Our TO, which consists of five indicators, was collected through the hospital elective system. Postoperative complications of grade II or higher, according to the Clavien-Dindo classification, were considered severe.

At present, there is no obvious distinction between surgical treatment strategies for mixed neuroendocrine-euroneuroendocrine neoplasms and neuroendocrine carcinoma (NEC) (21,22); hence, we combined them in the analysis. The staging was derived from the 8th American Joint Commission on Cancer (AJCC) criteria. According to the 2019 World Health Organization (WHO) classification (23,24), patients were sorted as G1 (Ki67≤2%), G2 (2%<Ki67≤20%), or G3 (Ki67>20%).

Overall survival (OS) was calculated from the date of surgery to death from any cause. Recurrence-free survival (RFS) was calculated from the date of surgery to loco-regional or distant recurrence due to any cause. Recurrence was defined by imaging evaluation, cytology, or tissue biopsy in combination with the clinical history and physical examination at the earliest date. Recurrence was diagnosed based on radiologic findings or biopsies of suspicious lesions, when possible. Disease-free survival (DFS) was calculated from the date of surgery to any loco-regional or distant recurrence, other primary tumors, or death from any cause. Postoperative follow-ups were performed every 3−6 months for the first 3 years, and then every 6−12 months from years 3 to 10. Most routine patient follow-up appointments included a physical examination, laboratory tests, chest radiography, abdominal ultrasonography or computed tomography (CT), and an annual endoscopic examination. The median follow-up time in this study was 55 months. The maximum follow-up date was October 2018. The medium follow-up time was 55 months.

Statistical analysis

A Student's *t* test or Mann-Whitney U test was used for continuous variables. We used a χ^2 test or Fisher's exact test to compare the categorical variables of the clinical characteristics. First, we calculated the number and proportion of patients for whom each outcome indicator was realized. Then we calculated the number and proportion of patients for whom each consecutive outcome indicator was realized (namely, those who simultaneously met the previous and subsequent metric criteria) (10). We estimated the median survival using the Kaplan-Meier method. The survival rates were then compared using a log-rank test. Landmark analysis for G-NEC patients was used to eliminate the immortal bias. The landmark time point was at day 31 of follow-up. The association of relevant clinicopathologic variables with OS, DFS, and RFS was assessed using a Cox proportional hazards model. We assessed the risk factors of non-Textbook Outcome (non-TO) using multivariate logistic regression analysis, incorporating other potential explanatory variables. Stepwise backward variable removal was applied to the multivariate model, to identify the most accurate set of predictors (25). The TO rate was considered a categorical variable. We calculated the TO rate among different hospitals and ranked these hospitals accordingly. The cut-off values were lower quartile−50% and upper quartile−60%. The centers were divided into three groups (TO≤50% group, 50%<TO≤60% group, and TO>60% group) to further analyze the relationship between TO and 5-year OS. Hospital volume was also considered a categorical variable and used ranking hospitals in order to increase total volume and select cut-off points in the interquartile range. Specifically, we applied the following distinction: low-volume (n≤50 patients), medium-volume (50 patients<n≤100 patients), and high-volume (n>100 patients) centers. Then we calculated three levels for the corresponding TO rates, and investigated the relationship among hospital volume, TO rate, and OS (15,26-28).

To analyze hospital variation in TO, case mix-adjusted hospital results were calculated. The possible associations between patient characteristics and TO were analyzed to subsequently adjust hospital TO rates for the case-mix factors. Therefore, patient and tumor characteristics were entered in a multivariate logistic regression model at a P-value of 0.05, using an ENTER model. To adjust for case-mix factors, several variables were analyzed including age, American Society of Anesthesiologists (ASA) score, surgical type, blood loss, and tumor location. Individual hospital results were displayed using funnel plots, combining scatter plots and a sequence of 95.0% and 99.8% confidence

intervals (95.0% CIs and 99.8% CIs) (29). To minimize statistical artefacts resulting from the small sample size, hospitals with <11 G-NEC resections were excluded from this analysis. We also performed risk-adjusted funnel plots of all hospitals to show the details of hospitals with <11 G-NEC resections.

Sankey plots were applied to analyze the relationship between different TO items and survival outcome. The survival status within Sankey plots was recorded until follow-up was completed. Statistical analyses were performed using IBM SPSS (Version 20.0; IBM Corp., New York, USA) and R software (Version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria). P<0.05 were considered statistically significant.

Results

General clinical and pathological data

Baseline characteristics for the TO and non-TO groups are presented in *Supplementary Table S1*. Altogether, 860 patients were included in the study; they were divided into a TO group (487 patients, 56.6%) and a non-TO group (373 patients, 43.4%). There were significant differences in period, age, ASA score, surgical type, blood loss, and tumor location (P<0.05). However, no significant differences in sex, body mass index (BMI), pT and pN stage, grade, tumor size, neoadjuvant chemotherapy, and chemotherapy were observed (P>0.05). In total, 23 (6.2%) patients did not achieve the R0 margin in the non-TO group.

TO after resection of G-NEC

In accordance with the methods, we individually calculated each quality metric: 97.3% (837/860 patients) achieved curative resection, 79.7% (685/860 patients) had ≥15 LNs examined, 80.6% (693/860 patients) had no severe postoperative complications, 87.1% (749/860 patients) had a hospital stay ≤21 d, and 98.6% (848/860 patients) had no hospital readmission ≤30 d after discharge. The quality metrics that had the most negative impact on the proportion achieving TO were ≥15 LNs examined and no severe postoperative complications, which occurred in only 79.7% and 80.6% of cases, respectively.

We then sequentially calculated the five quality metrics: curative resection was achieved in 97.3% of patients; curative resection and ≥15 LNs examined were achieved in 78.6%; curative resection, ≥15 LNs examined, and no severe postoperative complications was achieved in 62.9%; curative resection, ≥15 LNs examined, no severe postoperative complications, and postoperative hospital stay ≤21 d was achieved in 57.2%. Approximately, 56.6% of patients met all five TO quality metrics. Hence, 487 patients achieved TO (*Figure 1*).

Supplementary Figure S2 shows the changing trends of TO during different periods from 2005 to 2018. Except for a slightly lower TO rate from 2011–2013 than from 2008–2010, the TO rate gradually increased over time,

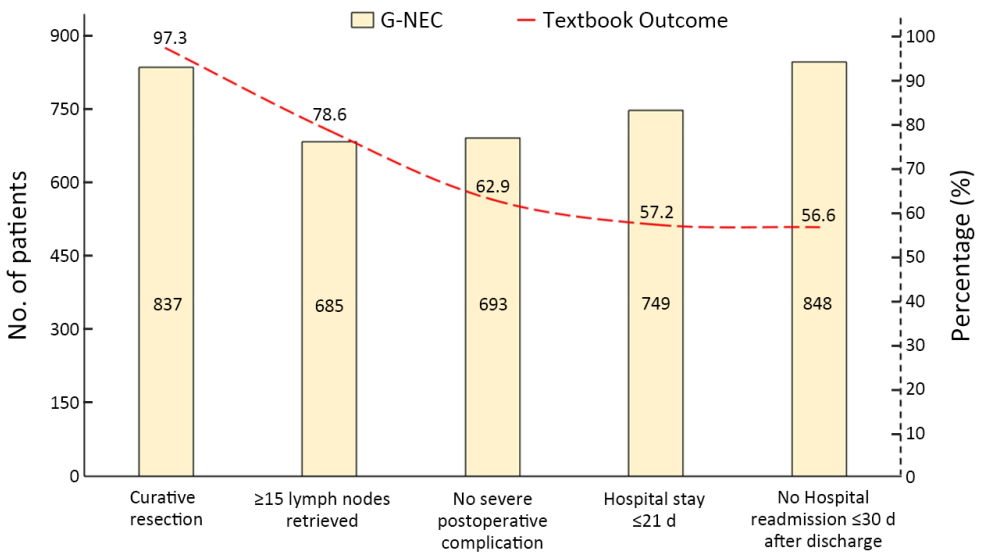

Figure 1 Textbook Outcome: a composite measure of outcome parameters in patients undergoing surgery for G-NEC. G-NEC, gastric neuroendocrine carcinoma.

with 2005–2007 showing the lowest TO rate (only 40%), and 2017–2018 showing the highest (72.7%).

Survival analysis

Survival curves revealed that OS, DFS, and RFS of TO patients were significantly better than those of non-TO patients (all P<0.05; *Figure 2*). Landmark analysis also showed that results of OS, DFS, and RFS of TO patients were consistent with Kaplan-Meier survival curves. Landmark analysis revealed that at day 31 of follow-up, OS, DFS, and RFS of TO patients were similar to those of non-TO patients (P>0.05). After the 31-day follow-up, OS, DFS, and RFS of TO patients were significantly better than those of non-TO patients (P<0.05) (*Supplementary Figure S3*). Because TO consists of five quality metrics, through the dynamic display function of the Sankey plot, the relationship between the five metrics and the individual's final survival status was displayed.

In *Figure 3*, G-NEC patients were gradually isolated when challenging each TO item individually. The prognostic outcomes of "Alive" mostly consisted of TO patients (62.2%) who definitely met the five metrics, and only the rest of "Alive" outcome (37.8%) were from non-TO patients (*Figure 3A*). Similarly, among the analysis of recurrence outcomes, the prognostic outcomes with "no recurrence" were mostly made up of TO patients (60.3%), whereas non-TO patients accounted for only 39.7% and presented no recurrence (*Figure 3B*). In this process, every additional unmet metric will be prone to a more dismal long-term outcome for the patients.

Considering the independent prognostic factors affecting prognosis (*Table 1*), Cox univariate analysis showed that TO, hospital volume, age, ASA score, tumor location and size, pT and pN stages, and G grade were factors significantly affecting the patients' OS (P<0.05). Further multivariate analyses revealed that overlapping location, higher pT stage, lymph node metastasis, and non-TO were independent risk factors for OS, but the medium-volume center (50<n≤100) was independent protective factors (P<0.05). In parallel, in G-NEC patients, non-TO was also an independent risk factor for both DFS and RFS (P<0.05) (*Supplementary Table S2*, *S3*).

Hospital volume, TO, and OS

Usually, single-center hospital volume is an important index for surgical quality assessment. However, for G-NEC, our multicenter study showed that high-volume centers did not stably reflect better long-term survival (*Figure 4A*). Even medium-volume centers presented a better OS than high-volume ones (P=0.036). However, by observing the relationship between TO and survival, it can be seen that as TO gradually increases, the long-term survival rate of patients can gradually increase (*Figure 4B*, *C*). As shown in *Supplementary Figure S4*, at day 31 of follow-up, there was no significant difference in OS among different volume hospitals and different levels of TO rates, respectively (P=0.210, P=0.312). After the 31-day follow-up, high-volume centers did not stably reflect better long-term survival, while medium-volume centers even presented a better OS. Hence, by comparing with TO, we found that the long-term survival of G-NEC patients improved with increasing TO rates. The three-dimensional stereoscopic diagram and funnel plot showed the relationship among different volumes, TO, and survival. When the hospital volume increased, the 5-year survival of G-NEC patients did not improve, and the hospital volume

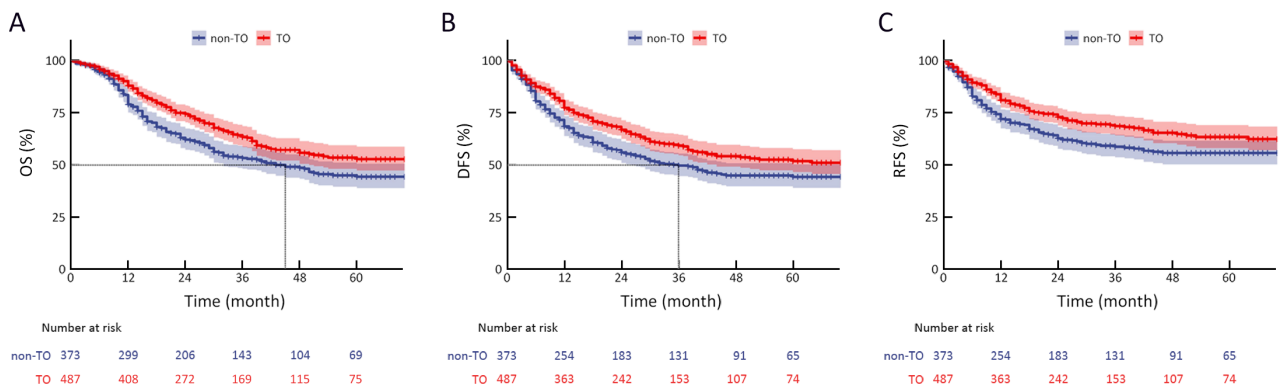

Figure 2 Prognosis of TO patients was superior to that of non-TO patients. (A) OS (P=0.003); (B) DFS (P=0.004); (C) RFS (P=0.005). TO, Textbook Outcome; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival.

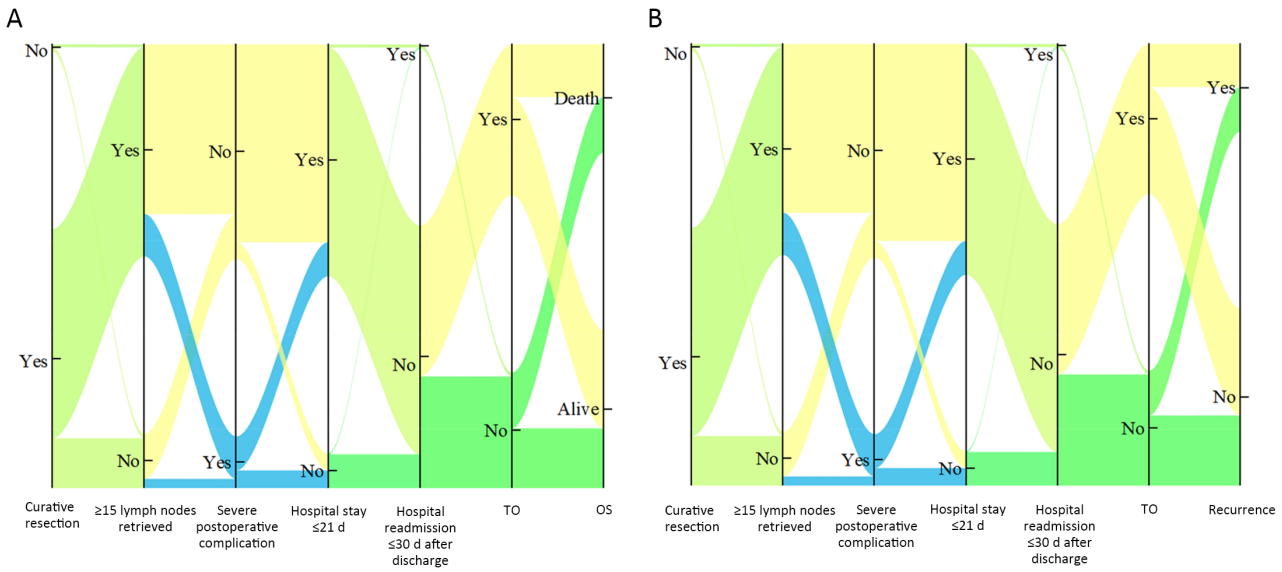

Figure 3 Sankey plot dynamically displays flow relationship between TO and its five different metrics, between TO and the final prognosis outcome. (A) TO flows to the survival outcome; (B) TO flows to the recurrence outcome. TO, Textbook Outcome; OS, overall survival.

level was not associated with 5-year survival (Pearson test, P=0.567; *Figure 5A*). However, with increasing TO rates, the 5-year survival of G-NEC patients improved (Pearson test, P=0.013).

TO rates for individual centers were adjusted by case-mix factors (*Figure 5B*). The adjusted TO rates ranged from 9.1% to 86.5% for G-NEC patients. With increasing numbers of cases, the TO rates did not significantly improve, suggesting that the realization rate of TO was not directly associated with the increasing hospital volume. *Supplementary Figure S5* shows the risk-adjusted performances of all hospitals. *Supplementary Table S4* shows the clinicopathologic description between medium- and high-volume centers.

TO-associated factors

To explore whether non-TO can be predicted preoperatively and intraoperatively, the logistic univariate analysis of risk factors for non-TO patients is shown in *Table 2*. According to this, age, ASA score, tumor location, surgical type, and blood loss were significant factors resulting in non-TO outcomes (P<0.05). Further multivariate analysis showed that non-lower tumors, open surgery, and blood loss >200 mL were independent risk factors for non-TO patients (P<0.05). The analysis of the risk factors affecting TO patients is shown in *Supplementary Table S5*. When the number of risk factors was 0, 1, 2, and 3, the proportion of TO patients was 75.4% (52/69), 63.9% (212/332), 50.8% (197/388), and 36.6% (26/71), respectively. With the accumulation of risk factors, the proportion of patients achieving TO significantly decreased (P<0.001).

Discussion

Although information on individual outcome indicators may be useful in evaluating medical quality improvement, it is difficult to compare hospital performance through individual indicators as a hospital may perform better in some than in others, since these parameters are often not related (10,16,30). The medical service level cannot be scientifically reflected by only one point; rather, it should be indicated by a comprehensive group of items. The evaluation of surgical treatments should be multidimensional. The Society for Thoracic Surgeons was one of the first to start a clinical audit to monitor their results (31,32). Then, O'Brien *et al*. developed and analyzed a method of composite scoring for cardiac surgery, which was described as the "all-or-none" method, and represented the base for our TO (33). This provided a feasible and informative indicator, suitable for comparison in multicenter studies. This work demonstrated the effectiveness of a composite indicator, consisting of five single parameters, in the assessment of medical treatments. Among G-NEC patients, 56.6% achieved TO. After adjusting for the case mix, we found that there were differences in TO rates among different centers, where the top rate reached 86.5%, but the lowest rate was only 9.1%.

Table 1 Univariate and multivariate Cox analysis of clinicopathological factors for OS

Clinical parameters	Event	Total	Univariable			Multivariable		
			HR	95% CI	P	HR	95% CI	P
TO								
No	180	373	Ref.			Ref.		
Yes	170	487	0.73	0.59–0.90	0.003	0.76	0.62–0.94	0.013
Period								
2005–2007	9	20	Ref.					
2008–2010	18	44	1.03	0.46–2.29	0.944			
2011–2013	134	240	1.54	0.78–3.02	0.210			
2014–2016	171	406	1.31	0.67–2.57	0.428			
2017–2018	18	150	0.85	0.38–1.92	0.700			
Hospital volume								
n≤50	139	289	Ref.			Ref.		
50<n≤100	75	233	0.57	0.43–0.76	<0.001	0.64	0.48–0.86	0.003
n>100	136	338	0.78	0.62–0.99	0.039	0.86	0.67–1.10	0.217
Age (year)								
≤65	181	478	Ref.					
>65	169	382	1.24	1.01–1.53	0.044			
Sex								
Female	69	187	Ref.					
Male	281	673	1.20	0.92–1.57	0.169			
ASA score								
I–II	289	731	Ref.					
III–V	42	82	1.49	1.07–2.05	0.017			
Unknown	19	47	1.05	0.66–1.67	0.836			
BMI (kg/m^2)								
<18.5	24	49	Ref.					
18.5–25.0	222	547	0.77	0.51–1.18	0.233			
>25.0	66	176	0.69	0.43–1.11	0.123			
Unknown	38	88	0.69	0.41–1.15	0.154			
Tumor location								
Upper	184	445	Ref.			Ref.		
Middle	46	146	0.75	0.54–1.03	0.075	0.84	0.60–1.15	0.274
Lower	94	220	1.03	0.80–1.32	0.822	1.24	0.97–1.60	0.092
Overlapping	26	49	1.53	1.02–2.31	0.042	1.55	1.03–2.35	0.036
Tumor size (cm)								
≤2	23	92	Ref.					
>2 and ≤5	183	472	1.56	1.01–2.41	0.044			
>5	144	296	2.27	1.46–3.52	<0.001			
T stage (the AJCC 8th)#								
T1	5	57	Ref.			Ref.		
T2	20	81	3.45	1.29–9.18	0.013	2.96	1.11–7.92	0.031

Table 1 (*continued*)

Table 1 (*continued*)

Clinical parameters	Event	Total	Univariable			Multivariable		
			HR	95% CI	P	HR	95% CI	P
T3	50	164	4.12	1.64–10.34	0.003	3.57	1.41–9.06	0.007
T4	275	558	7.46	3.08–18.08	<0.001	5.87	2.39–14.37	0.000
N stage (the AJCC 8th)[##]								
N0	62	236	Ref.			Ref.		
N+	288	624	1.99	1.51–2.62	<0.001	1.68	1.27–2.22	<0.001
Grade (WHO 2010)								
G1/G2	18	68	Ref.					
G3	332	792	1.73	1.08–2.78	0.024			
Neoadjuvant chemotherapy								
No	340	836	Ref.					
Yes	10	24	1.25	0.67–2.35	0.484			
Chemotherapy								
No	117	331	Ref.					
Yes	233	529	1.24	0.99–1.55	0.058			

OS, overall survival; TO, Textbook Outcome; ASA, American Society of Anesthesiologists; BMI, body mass index; AJCC, American Joint Commission on Cancer; WHO, World Health Organization; HR, hazard ratio; 95% CI, 95% confidence interval; [#], T stage is classified by AJCC 8th and T4 contains T4a and T4b; [##], N stage is classified by AJCC 8th; N+ stages contain N1, N2, N3a and N3b. n of hospital volume: the First Hospital Affiliated to Soochow University (n=5); Renji Hospital, Shanghai Jiaotong University (n=9); Zhangzhou Affiliated Hospital of Fujian Medical University (n=3); the First Affiliated Hospital of Nanjing Medical University (n=7); Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine (n=5); Provincial Clinical Medical College of Fujian Medical University, Fujian Provincial Hospital (n=19); Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences (n=2); the Second People's Hospital of Liaocheng (n=9); Meizhou People's Hospital (n=1); the Second Affiliated Hospital, Nanchang University (n=2); Tianjin Medical University General Hospital (n=11); Quanzhou First Hospital Affiliated to Fujian Medical University (n=7); Huashan Hospital, Fudan University (n=96); the First Affiliated Hospital of Anhui Medical University (n=57); Affiliated Hospital of Qingdao University (n=37); West District of the First Affiliated Hospital of University of Science and Technology of China (n=151); Yantai Yuhuangding Hospital (n=40); Fujian Medicine University Teaching Hospital, the First Hospital of Putian (n=33); Fujian Medical University Union Hospital (n=187); National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (n=53); the Affiliated Hospital of Putian University (n=42); the First Affiliated Hospital of Fujian Medical University (n=84).

Funnel plots indicated that TO rates were not enhanced with increasing hospital volume, implying no direct association between them. When analyzing the relationship between hospital volume and survival, the prognosis within medium-volume centers was better than within low- and high-volume centers. Based on previous experience, increasing numbers of surgical cases are often accompanied by enhanced surgery quality, thereby improving prognosis for patients. Due to the specificity of G-NEC, the prognosis for such patients did not significantly improve with hospital volume, which is significantly different compared with common GC (26,27,34,35). For patients undergoing curative G-NEC surgery, the surgical process can be considered safe if no adverse outcomes (severe postoperative complications, prolonged hospital stay, and readmission) have occurred, and effective if complete tumor removal and adequate lymphadenectomy have been achieved. These parameters have been included in the definition of TO. Our results showed that failure in retrieving at least 15 LNs and severe postoperative complications had the greatest negative impact on TO for G-NEC patients. Therefore, for clinical surgeons, it will be paramount to improve the level of intraoperative LN dissection and reduce the incidence of severe postoperative complications. Simultaneously, a better understanding of different factors that lead to TO success or failure may potentially help health service providers to further improve postoperative management and care quality, as well as to reduce hospital costs (36,37). Altogether, TO provides caregivers with important information on patient therapeutic feedback, and this may drive quality improvements in hospitals. For patients, TO also discloses more information and available choices for favorable outcomes, thereby selecting specific care-service resources.

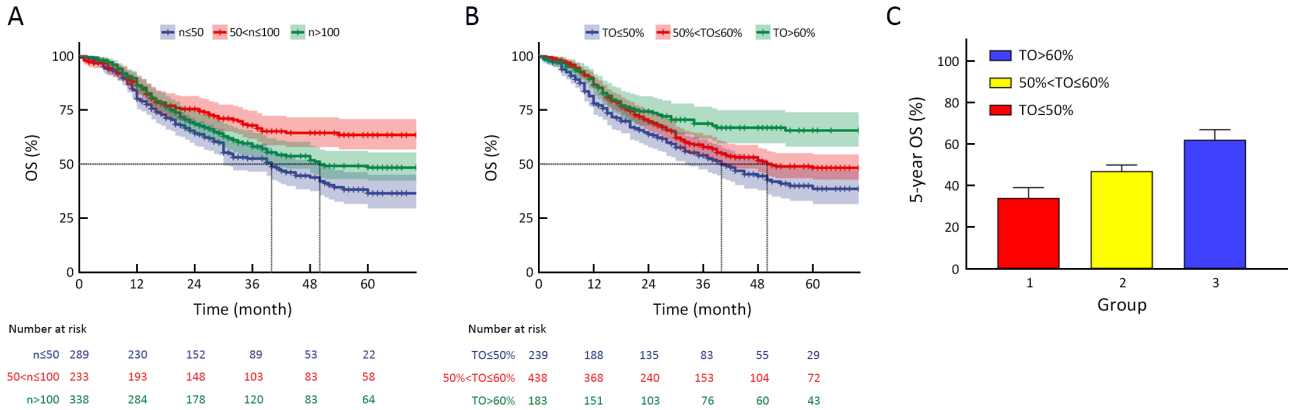

Figure 4 Relationship among different hospital volumes, TO, and OS. (A) OS of patients within different hospital volumes ($P_{n\leq 50}$ *vs.* $_{50<n\leq 100}$=0.036; $P_{50<n}$ *vs.* $_{n>100}$<0.001; $P_{50<n\leq 100}$ *vs.* $_{n>100}$=0.038); (B) OS of patients within different TO rates ($P_{TO\leq 50\%}$ *vs.* $_{50\%<TO\leq 60\%}$=0.030; $P_{TO\leq 50\%}$ *vs.* $_{TO>60\%}$<0.001; $P_{50\%<TO\leq 60\%}$ *vs.* $_{TO>60\%}$=0.023); (C) 5-year OS of patients within different TO rates (P=0.006). TO, Textbook Outcome; OS, overall survival.

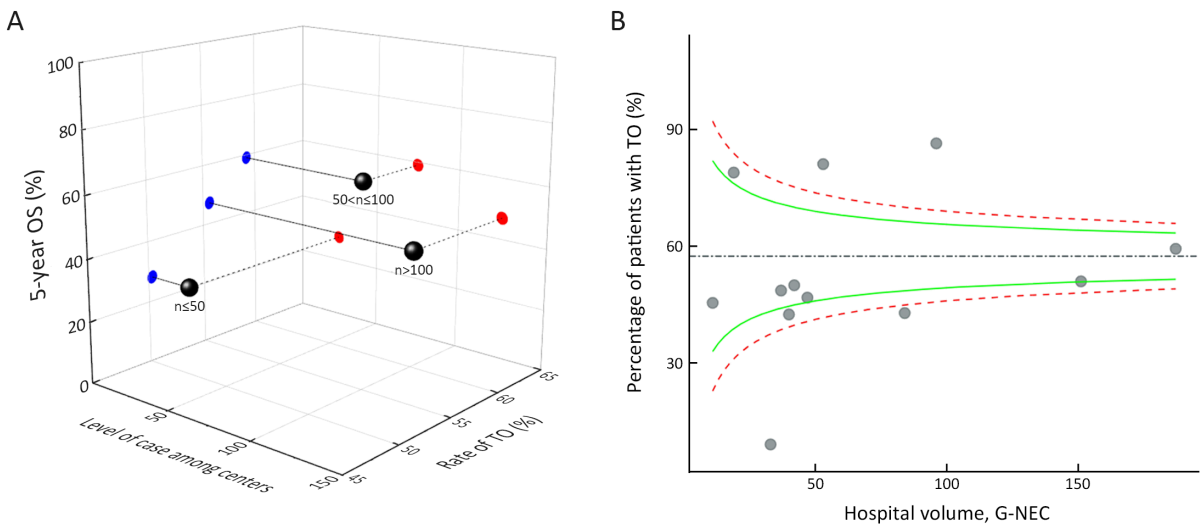

Figure 5 Relationship among hospital volumes, TO rate, and 5-year OS. (A) Three-dimensional stereoscopic diagram. The red dots represent the projection from the hospital volume ("n", in the XZ plane; coordinate system of the hospital volume and 5-year OS). OS within the three levels was not improved with increasing levels of hospital volume. Pearson test revealed no association between hospital volume and 5-year OS (P=0.567). The blue dots represent the projection from different TO rates ("n", in the YZ plane; coordinate system of the TO rate and 5-year OS). OS within three groups was improved with increasing TO rate. Pearson test revealed a significant association between TO rate and 5-year OS (P=0.013); (B) Hospital variation in risk-adjusted percentages of TO. The gray dots indicate individual institutions, the green solid lines and red dotted lines indicate the 95% and 99.8% CIs, respectively. To minimize statistical artefacts because of the small sample size, hospitals with <11 G-NEC resections were excluded from this analysis. TO, Textbook Outcome; OS, overall survival; 95% and 99.8% CIs, 95% and 99.8% confidence intervals; G-NEC, gastric neuroendocrine carcinoma.

For hospitals, TO provides information on how often treatment is successful and may drive quality improvement. TO may be useful in selective contracting as it summarizes indicators of patient safety, effectiveness, and efficiency.

NEC is a higher malignant degree type of gastric neuroendocrine neoplasm, whose incidence and morbidity increase every year (38,39). Currently, among the prognostic factors associated with G-NEC, the most recognized index includes Ki67 and a constantly updated TNM stage (4,5). However, the above information is generally retrieved from tumor pathology and anatomy. Although many studies reported the effects of surgery on

Table 2 Logistic regression analysis factors associated with non-TO

Clinical parameters	Univariable			Multivariable		
	OR	95% CI	P	OR	95% CI	P
Hospital volume						
n≤50	Ref.					
50<n≤100	0.87	0.61–1.23	0.419			
n>100	1.01	0.73–1.38	0.982			
Age (year)						
≤65	Ref.					
>65	1.32	1.01–1.73	0.048			
Sex						
Female	Ref.					
Male	0.98	0.70–1.35	0.881			
ASA score						
I–II	Ref.					
III–V	0.93	0.58–1.47	0.741			
Unknown	0.43	0.22–0.83	0.013			
BMI (kg/m^2)						
<18.5	Ref.					
18.5–25.0	0.99	0.55–1.78	0.969			
>25.0	0.91	0.48–1.72	0.775			
Unknown	0.70	0.34–1.43	0.328			
Tumor location						
Lower	Ref.			Ref.		
Non-lower	1.69	1.22–2.32	0.001	1.73	1.25–2.39	0.001
Surgical type						
Laparoscopy/Robotic surgery	Ref.			Ref.		
Open	1.72	1.29–2.30	<0.001	1.63	1.21–2.20	0.001
Other	0.74	0.14–3.88	0.722	0.68	0.13–3.66	0.684
Blood loss (mL)						
<100	Ref.			Ref.		
100–200	1.23	0.88–1.73	0.222	1.10	0.78–1.56	0.589
>200	2.25	1.57–3.24	<0.001	2.07	1.43–3.00	<0.001
Tumor size (cm)						
≤2	Ref.					
>2 and ≤5	1.06	0.68–1.67	0.796			
>5	1.02	0.64–1.64	0.931			
T stage (the AJCC 8th)#						
T1	Ref.					
T2	1.31	0.66–2.59	0.445			
T3	0.83	0.45–1.54	0.556			
T4	1.23	0.70–2.14	0.471			

Table 2 (*continued*)

Table 2 (*continued*)

Clinical parameters	Univariable			Multivariable		
	OR	95% CI	P	OR	95% CI	P
N stage (the AJCC 8th)[##]						
N0	Ref.					
N+	1.06	0.78–1.43	0.716			
Grade (WHO 2010)						
G1	Ref.					
G2	1.57	0.52–4.71	0.420			
G3	1.19	0.46–3.10	0.724			
Neoadjuvant chemotherapy						
No	Ref.					
Yes	0.78	0.34–1.80	0.557			

TO, Textbook Outcome; ASA, American Society of Anesthesiologists; BMI, body mass index; AJCC, American Joint Commission on Cancer; WHO, World Health Organization; HR, hazard ratio; 95% CI, 95% confidence interval; [#], T stage is classified by AJCC 8th and T4 contains T4a and T4b; [##], N stage is classified by AJCC 8th; N+ stages contain N1, N2, N3a and N3b. n of hospital volume: the First Hospital Affiliated to Soochow University (n=5); Renji Hospital, Shanghai Jiaotong University (n=9); Zhangzhou Affiliated Hospital of Fujian Medical University (n=3); the First Affiliated Hospital of Nanjing Medical University (n=7); Ruijin Hospital affiliated to Shanghai Jiaotong University School of Medicine (n=5); Provincial Clinical Medical College of Fujian Medical University, Fujian Provincial Hospital (n=19); Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences (n=2); the Second People's Hospital of Liaocheng (n=9); Meizhou People's Hospital (n=1); the Second Affiliated Hospital, Nanchang University (n=2); Tianjin Medical University General Hospital (n=11); Quanzhou First Hospital Affiliated to Fujian Medical University (n=7); Huashan Hospital, Fudan University (n=96); the First Affiliated Hospital of Anhui Medical University (n=57); Affiliated Hospital of Qingdao University (n=37); West district of the First Affiliated Hospital of University of Science and Technology of China. (n=151); Yantai Yuhuangding Hospital (n=40); Fujian Medicine University Teaching Hospital, the First Hospital of PuTian (n=33); Fujian Medical University Union Hospital (n=187); National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (n=53); the Affiliated Hospital of Putian University (n=42); the First Affiliated Hospital of Fujian Medical University (n=84).

the prognosis of NEC, the combination of surgical quality and postoperative management, namely, the impact of TO on long-term prognosis, has not been evaluated. Our results showed that TO was an independent risk factor for G-NEC patients. Survival analysis showed that the prognosis of TO patients was significantly better than that of non-TO patients. Furthermore, an escalating TO rate was strongly associated with improved survival, implying that successful operation and careful postoperative management were related to the long-term outcomes of patients. In the study, factors related to tumor and surgery affected the likelihood of achieving TO after G-NEC gastrectomy. More precisely, risk-related factors that may increase the probability of non-TO included non-lower tumors, open surgery, and >200 mL blood loss. Tumors located in the non-lower part of the stomach may implicate a wider range gastrectomy, such as a total gastrectomy, with a possible upgrade of the operation difficulty. Compared with minimally invasive procedures, such as laparoscopy or robotic surgery, open surgery implies a larger surgical incision, leading to greater damage, which would be detrimental to postoperative early recovery. Finally, excessive blood loss during surgery will increase the postoperative recovery time, reducing the probability of achieving TO. A clinical surgeon should identify patients with high-risk factors and develop more detailed treatment options for them. TO encloses the acknowledged prognostic factors, including radical resection, adequate LN dissection, and no severe postoperative complications. The prognostic value of the dissection of at least 15 LNs for GC patients has already been proven by many researchers (40-44). Severe postoperative complications may also play a role in long-term survival. Anastomotic leakage and infectious complications are associated with disease recurrence in various tumor types (45-49).

To our knowledge, this is the first study on a composite evaluation measure for surgical quality and comprehensive predictor for long-term outcome in rare cancers. It included a large amount of data and long-term follow-up. However, some limitations exist. Firstly, other data, such as those on targeting and endocrine treatment were incomplete, which may have inevitably caused some bias.

Furthermore, there is no acknowledged definition of TO; thus, selecting different measures of surgical quality indicators may lead to different outcomes. Lastly, because of their composition, the five TO metrics could possibly be refined by adding weights to different outcome measures, making some outcomes more important than others. However, no clear evidence or resource from which to derive this weight is available. Therefore, any weights added to the TO metrics would be subjective and diminish its simplicity and usefulness (10).

Moreover, this study only included five items of TO, yet the multi-center results demonstrated the values of TO in the surgical quality control and long-term prognosis for G-NEC. Such a complex indicator TO was characteristic of easy promotion and high reproducibility in the real world. It is worth noting that TO is not designed to replace the individual quality indicators, but is meant as an addition to them. Considering medical and surgical complexity and specific differences among individual patients, our results do not imply that patients who did not meet all TO indicators received incorrect treatment. In the future, we look forward to exploring more clinical studies on the surgical treatment of GC and related rare diseases by combining hospitals with different volumes in China to validate our findings.

Conclusions

Hospital volume was not a good indicator for assessing surgical quality of G-NEC. TO is strongly associated with multicenter surgical quality and prognosis for G-NEC patients. Factors predicting non-TO are identified, which may help guide strategies to optimize G-NEC outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006; 118:3030-44.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
3. Delle Fave G, O'Toole D, Sundin A, et al. ENETS consensus guidelines update for gastroduodenal neuroendocrine neoplasms. Neuroendocrinology 2016;103:119-24.
4. Shah MH, Goldner WS, Halfdanarson TR, et al. NCCN Guidelines Insights: Neuroendocrine and Adrenal Tumors, Version 2.2018. J Natl Compr Canc Netw 2018;16:693-702.
5. Garcia-Carbonero R, Sorbye H, Baudin E, et al. Consensus guidelines for high grade gastro-entero-pancreatic (GEP) neuroendocrine tumours and neuroendocrine carcinomas (NEC). Neuroendocrinology 2016;103:586-91.
6. Tan YE, Wang PL, Yin SC, et al. Thirty-year trends in clinicopathologic characteristics and prognosis after gastrectomy for gastric cancer: A single institution in Northern China. J Cancer 2020;11:1056-62.
7. Nakamura K, Ueyama T, Yao T, et al. Pathology and prognosis of gastric carcinoma. Findings in 10,000 patients who underwent primary gastrectomy. Cancer 1992;70:1030-7.
8. Vanoli A, La Rosa S, Miceli E, et al. Prognostic evaluations tailored to specific gastric neuroendocrine neoplasms: Analysis of 200 cases with extended follow-up. Neuroendocrinology 2018;107:114-26.
9. La Rosa S, Inzani F, Vanoli A, et al. Histologic characterization and improved prognostic evaluation of 209 gastric neuroendocrine neoplasms. Hum Pathol 2011;42:1373-84.
10. Kolfschoten NE, Kievit J, Gooiker GA, et al. Focusing on desired outcomes of care after colon cancer resections; hospital variations in "textbook outcome". Eur J Surg Oncol 2013;39:156-63.
11. Lin J, Zhao Y, Zhou Y, et al. Which staging system is more suitable for gastric neuroendocrine cancer and mixed adenoneuroendocrine carcinomas? A multi-center cohort study. Neuroendocrinology 2020 [Online ahead of print].

12. Lu J, Zhao YJ, Zhou Y, et al. Modified staging system for gastric neuroendocrine carcinoma based on American Joint Committee on Cancer and European Neuroendocrine Tumor Society systems. Br J Surg 2020;107:248-57.
13. Busweiler LA, Schouwenburg MG, van Berge Henegouwen MI, et al. Textbook outcome as a composite measure in oesophagogastric cancer surgery. Br J Surg 2017;104:742-50.
14. van der Kaaij RT, de Rooij MV, van Coevorden F, et al. Using textbook outcome as a measure of quality of care in oesophagogastric cancer surgery. Br J Surg 2018;105:561-9.
15. Levy J, Gupta V, Amirazodi E, et al. Gastrectomy case volume and textbook outcome: an analysis of the Population Registry of Esophageal and Stomach Tumours of Ontario (PRESTO). Gastric Cancer 2020;23:391-402.
16. Karthaus EG, Lijftogt N, Busweiler LAD, et al. Textbook Outcome: A composite measure for quality of elective aneurysm surgery. Ann Surg 2017;266: 898-904.
17. Merath K, Chen Q, Bagante F, et al. A multi-institutional international analysis of Textbook Outcomes among patients undergoing curative-intent resection of intrahepatic cholangiocarcinoma. JAMA Surg 2019;154:e190571.
18. Heidsma CM, Hyer M, Tsilimigras DI, et al. Incidence and impact of Textbook Outcome among patients undergoing resection of pancreatic neuroendocrine tumors: Results of the US Neuroendocrine Tumor Study Group. J Surg Oncol 2020;121:1201-8.
19. Mehta R, Paredes AZ, Tsilimigras DI, et al. Influence of hospital teaching status on the chance to achieve a textbook outcome after hepatopancreatic surgery for cancer among Medicare beneficiaries. Surgery 2020;168:92-100.
20. Mehta R, Tsilimigras DI, Paredes AZ, et al. Dedicated cancer centers are more likely to achieve a Textbook Outcome following hepatopancreatic surgery. Ann Surg Oncol 2020;27:1889-97.
21. La Rosa S, Marando A, Sessa F, et al. Mixed adenoneuroendocrine carcinomas (MANECs) of the gastrointestinal tract: An update. Cancers (Basel) 2012;4:11-30.
22. Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol 2018;31:1770-86.
23. Fléjou JF. WHO Classification of digestive tumors: the fourth edition. Ann Pathol (in French) 2011; 31(5 suppl):S27-31.
24. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76:182-8.
25. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515-26.
26. Hannan EL, Radzyner M, Rubin D, et al. The influence of hospital and surgeon volume on in-hospital mortality for colectomy, gastrectomy, and lung lobectomy in patients with cancer. Surgery 2002;131:6-15.
27. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128-37.
28. Finlayson EV, Goodney PP, Birkmeyer JD. Hospital volume and operative mortality in cancer surgery: a national study. Arch Surg 2003;138:721-5.
29. Mayer EK, Bottle A, Aylin P, et al. What is the role of risk-adjusted funnel plots in the analysis of radical cystectomy volume-outcome relationships? BJU Int 2011;108:844-50.
30. Parina RP, Chang DC, Rose JA, et al. Is a low readmission rate indicative of a good hospital? J Am Coll Surg 2015;220:169-76.
31. Clark RE. The development of The Society of Thoracic Surgeons voluntary national database system: genesis, issues, growth, and status. Best Pract Benchmarking Healthc 1996;1:62-9.
32. Shahian DM, Edwards FH, Ferraris VA, et al. Quality measurement in adult cardiac surgery: part 1 — Conceptual framework and measure selection. Ann Thorac Surg 2007;83(4 suppl):S3-12.
33. O'Brien SM, Shahian DM, DeLong ER, et al. Quality measurement in adult cardiac surgery: part 2 — Statistical considerations in composite measure scoring and provider rating. Ann Thorac Surg 2007;83(4 suppl):S13-26.
34. Callahan MA, Christos PJ, Gold HT, et al. Influence of surgical subspecialty training on in-hospital

mortality for gastrectomy and colectomy patients. Ann Surg 2003;238:629-36.
35. Smith DL, Elting LS, Learn PA, et al. Factors influencing the volume-outcome relationship in gastrectomies: a population-based study. Ann Surg Oncol 2007;14:1846-52.
36. Nolan T, Berwick DM. All-or-none measurement raises the bar on performance. JAMA 2006;295: 1168-70.
37. Reeves D, Campbell SM, Adams J, et al. Combining multiple indicators of clinical quality: an evaluation of different analytic approaches. Med Care 2007;45: 489-96.
38. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063-72.
39. Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. Lancet Oncol 2017;18:525-34.
40. Hartgrink HH, van de Velde CJ, Putter H, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. J Clin Oncol 2004; 22:2069-77.
41. Mirkin KA, Hollenbeak CS, Wong J. Greater lymph node retrieval improves survival in node-negative resected gastric cancer in the United States. J Gastric Cancer 2017;17:306-18.
42. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. J Clin Oncol 2005;23:7114-24.
43. Shen Z, Ye Y, Xie Q, et al. Effect of the number of lymph nodes harvested on the long-term survival of gastric cancer patients according to tumor stage and location: a 12-year study of 1,637 cases. Am J Surg 2015;210:431-40.
44. Sobin LH GM, Wittekind C (eds). International Union Against Cancer (UICC). TNM Classification of Malignant Tumours (7th edition). Wiley-Blackwell: New York, 2010.
45. Kofoed SC, Calatayud D, Jensen LS, et al. Intrathoracic anastomotic leakage after gastro-esophageal cancer resection is associated with increased risk of recurrence. J Thorac Cardiovasc Surg 2015;150:42-8.
46. Alonso S, Pascual M, Salvans S, et al. Postoperative intra-abdominal infection and colorectal cancer recurrence: a prospective matched cohort study of inflammatory and angiogenic responses as mechanisms involved in this association. Eur J Surg Oncol 2015;41:208-14.
47. Hayashi T, Yoshikawa T, Aoyama T, et al. Impact of infectious complications on gastric cancer recurrence. Gastric Cancer 2015;18:368-74.
48. Wu Y, Zhou BP. Inflammation: a driving force speeds cancer metastasis. Cell Cycle 2009;8:3267-73.
49. Lerut T, Moons J, Coosemans W, et al. Postoperative complications after transthoracic esophagectomy for cancer of the esophagus and gastroesophageal junction are correlated with early cancer recurrence: role of systematic grading of complications using the modified Clavien classification. Ann Surg 2009;250: 798-807.

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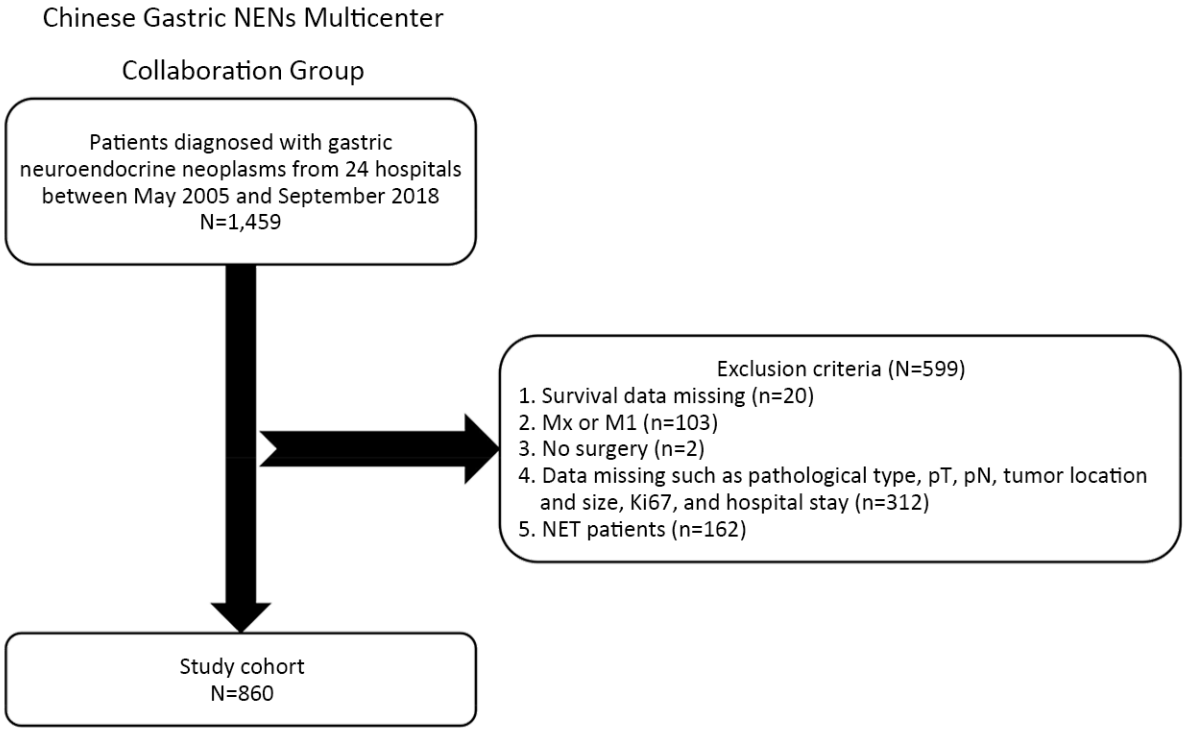

Figure S1 Patient flow diagram. NET, neuroendocrine tumor.

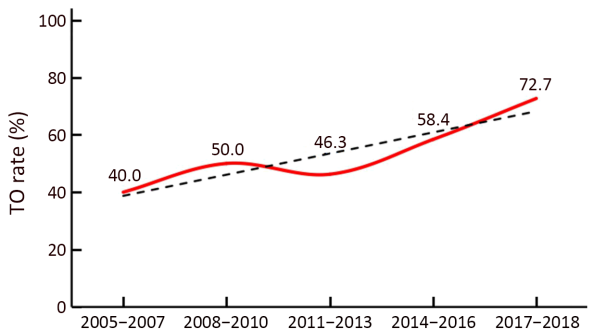

Figure S2 Trends of TO rates from 2005 to 2018. TO, Textbook Outcome.

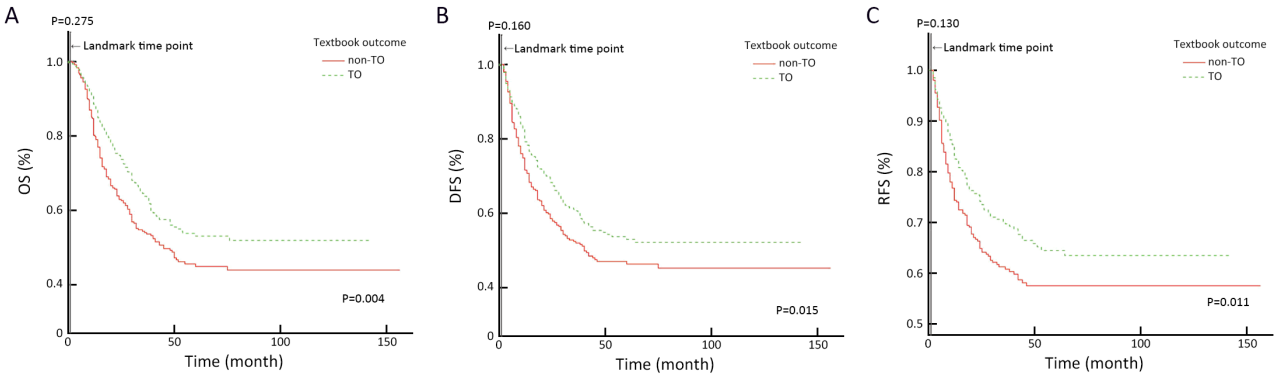

Figure S3 Landmark analysis of discriminating between events occurring before and after 31 d of follow-up. (A) OS ($P_{\text{before the landmark time point}}$=0.275, $P_{\text{after the landmark time point}}$=0.004); (B) DFS ($P_{\text{before the landmark time point}}$=0.160, $P_{\text{after the landmark time point}}$=0.015); (C) RFS ($P_{\text{before the landmark time point}}$=0.130, $P_{\text{after the landmark time point}}$=0.011). OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival.

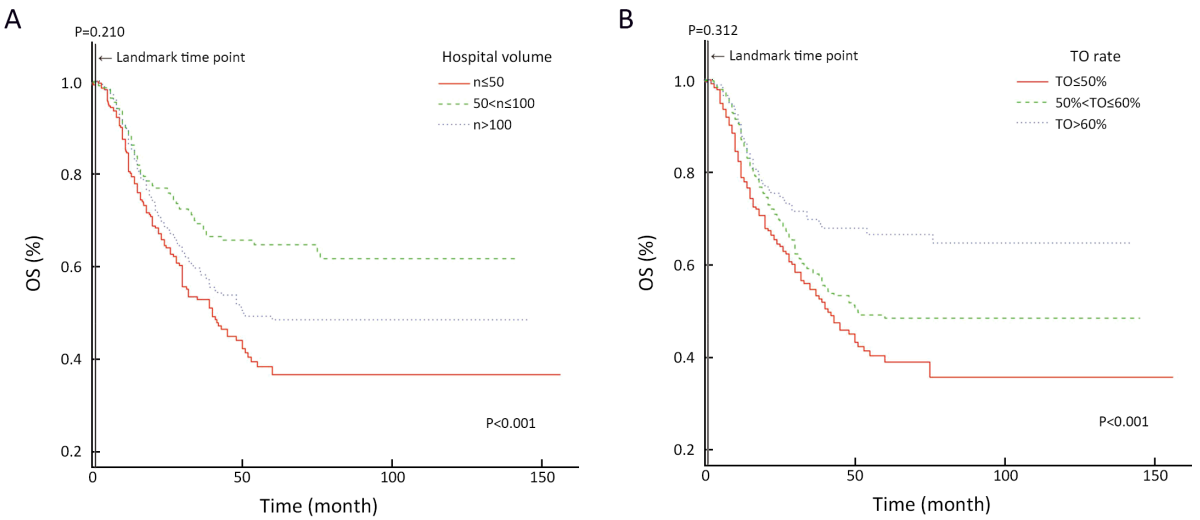

Figure S4 Landmark analysis among different hospital volumes, TO, and OS. (A) OS of patients within different hospital volumes ($P_{\text{before the landmark time point}}$=0.210, $P_{\text{after the landmark time point}}$<0.001, $P_{n\leq 50 \textit{ vs. } 50<n\leq 100}$=0.038; $P_{n\leq 50 \textit{ vs. } n>100}$<0.001; $P_{50<n\leq 100 \textit{ vs. } n>100}$=0.040); (B) OS of patients within different TO rates ($P_{\text{before the landmark time point}}$=0.312, $P_{\text{after the landmark time point}}$<0.001, $P_{TO\leq 50\% \textit{ vs. } 50\%<TO\leq 60\%}$=0.033; $P_{TO\leq 50\% \textit{ vs. } TO>60\%}$<0.001; $P_{50\%<TO\leq 60\% \textit{ vs. } TO>60\%}$=0.025). TO, Textbook Outcome; OS, overall survival.

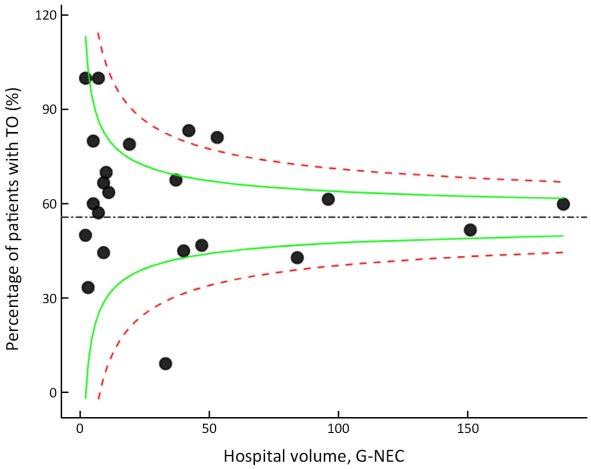

Figure S5 Hospital variation in risk-adjusted percentages of TO. Black dots indicate individual institutions and green solid lines and red dotted lines indicate 95% and 99.8% CIs, respectively. TO, Textbook Outcome; G-NEC, gastric neuroendocrine carcinoma; 95% and 99.8% CIs, 95% and 99.8% confidence intervals.

Table S1 Clinicopathologic description of all G-NEC patients (N= 860)

Variables	NECs [n (%)]		P
	Non-TO	TO	
Total	373 (43.4)	487 (56.6)	
Period			<0.001
2005	1 (0.3)	1 (0.2)	
2006	2 (0.5)	2 (0.4)	
2007	9 (2.4)	5 (1.0)	
2008	5 (1.3)	2 (0.4)	
2009	4 (1.1)	7 (1.4)	
2010	13 (3.5)	13 (2.7)	
2011	36 (9.7)	33 (6.8)	
2012	45 (12.1)	36 (7.4)	
2013	48 (12.9)	42 (8.6)	
2014	66 (17.7)	64 (13.1)	
2015	53 (14.2)	78 (16.0)	
2016	50 (13.4)	95 (19.5)	
2017	30 (8.0)	77 (15.8)	
2018	11 (2.9)	32 (6.6)	
Age (year)			0.047
≤65	193 (51.7)	285 (58.5)	
>65	180 (48.3)	202 (41.5)	
Sex			0.881
Female	82 (22.0)	105 (21.6)	
Male	291 (78.0)	382 (78.4)	
BMI (kg/m^2)			0.534
<18.5	22 (5.9)	27 (5.5)	
18.5–25.0	244 (65.4)	303 (62.2)	
>25.0	75 (20.1)	101 (20.7)	
Unknown	32 (8.6)	56 (11.5)	
ASA score			0.038
I–II	326 (87.4)	405 (83.2)	
III–V	35 (9.4)	47 (9.7)	
Unknown	12 (3.2)	35 (7.2)	
Surgical type			<0.001
Open	264 (70.8)	284 (58.3)	
Laparoscopy/ Robotic surgery	107 (28.7)	198 (40.7)	
Other	2 (0.5)	5 (1.0)	
Blood loss (mL)			<0.001
<100	198 (53.1)	315 (64.7)	
100–200	83 (22.3)	107 (22.0)	
>200	92 (24.7)	65 (13.3)	
Tumor location			0.015
Upper	206 (55.2)	239 (49.1)	
Middle	69 (18.5)	77 (15.8)	
Lower	75 (20.1)	145 (29.8)	
Overlapping	23 (6.2)	26 (5.3)	
T stage (the AJCC 8th)#			0.161
T1	23 (6.2)	34 (7.0)	
T2	38 (10.2)	43 (8.8)	
T3	59 (15.8)	105 (21.6)	
T4	253 (67.8)	305 (62.6)	
N stage (the AJCC 8th)##			0.716
N0	100 (26.8)	136 (27.9)	
N+	273 (73.2)	351 (72.1)	
Grade (WHO 2010)			0.585
G1	7 (1.9)	11 (2.3)	
G2	25 (6.7)	25 (5.1)	
G3	341 (91.4)	451 (92.6)	
Tumor size (cm)			0.948
≤2	39 (10.5)	53 (10.9)	
>2 and ≤5	207 (55.5)	265 (54.4)	
>5	127 (34.0)	169 (34.7)	
R0 margin			/
No	23 (6.2)	0 (0)	
Yes	350 (93.8)	487 (100)	
Neoadjuvant chemotherapy			0.556
No	364 (97.6)	472 (96.9)	
Yes	9 (2.4)	15 (3.1)	
Chemotherapy			0.717
No	141 (37.8)	190 (39.0)	
Yes	232 (62.2)	297 (61.0)	
Follow-up (month) [Median (range)]	55 (1–156)		

G-NEC, gastric neuroendocrine carcinoma; BMI, body mass index; ASA, American Society of Anesthesiologists; AJCC, American Joint Commission on Cancer; WHO, World Health Organization; NEC, neuroendocrine carcinoma; TO, Textbook Outcome; #, T stage is classified by AJCC 8th and T4 contains T4a and T4b; ##, N stage is classified by AJCC 8th. N+ stages contain N1, N2, N3a and N3b.

Table S2 Univariate and multivariate Cox analysis of clinicopathological factors for DFS

Clinical parameters	Event	Total	Univariable			Multivariable		
			HR	95% CI	P	HR	95% CI	P
TO								
No	189	373	Ref.			Ref.		
Yes	189	487	0.75	0.61–0.92	0.005	0.78	0.64–0.96	0.018
Period								
2005–2007	9	20	Ref.					
2008–2010	18	44	0.96	0.43–2.14	0.918			
2011–2013	139	240	1.56	0.80–3.06	0.196			
2014–2016	190	406	1.31	0.67–2.56	0.429			
2017–2018	22	150	0.65	0.30–1.43	0.285			
Hospital volume								
n≤50	149	289	Ref.			Ref.		
50<n≤100	83	233	0.59	0.45–0.77	<0.001	0.64	0.49–0.84	0.001
n>100	146	338	0.77	0.62–0.97	0.027	0.83	0.65–1.05	0.110
Age (year)								
≤65	193	478	Ref.					
>65	185	382	1.27	1.04–1.55	0.021			
Sex								
Female	72	187	Ref.					
Male	306	673	1.28	0.99–1.65	0.064			
ASA score								
I–II	311	731	Ref.					
III–V	44	82	1.44	1.05–1.98	0.023			
Unknown	23	47	1.15	0.75–1.76	0.520			
BMI (kg/m^2)								
<18.5	27	49	Ref.					
18.5–25.0	241	547	0.76	0.51–1.14	0.182			
>25.0	69	176	0.65	0.42–1.01	0.055			
Unknown	41	88	0.69	0.42–1.11	0.127			
Tumor location								
Upper	199	445	Ref.					
Middle	50	146	0.74	0.54–1.00	0.053			
Lower	103	220	1.06	0.83–1.34	0.658			
Overlapping	26	49	1.38	0.92–2.08	0.123			
Tumor size (cm)								
≤2	24	92	Ref.					
>2 and ≤5	200	472	1.70	1.12–2.60	0.014			
>5	154	296	2.42	1.57–3.72	<0.001			
T stage (the AJCC 8th)[#]								
T1	6	57	Ref.			Ref.		
T2	21	81	2.94	1.19–7.27	0.020	2.51	1.01–6.23	0.048

Table S2 (*continued*)

Table S2 (*continued*)

Clinical parameters	Event	Total	Univariable			Multivariable		
			HR	95% CI	P	HR	95% CI	P
T3	55	164	3.81	1.64–8.84	0.002	2.90	1.24–6.79	0.014
T4	296	558	6.82	3.04–15.32	<0.001	4.65	2.05–10.53	<0.001
N stage (the AJCC 8th)[##]								
N0	67	236	Ref.			Ref.		
N+	311	624	2.04	1.57–2.66	<0.001	1.78	1.36–2.33	<0.001
Grade (WHO 2010)								
G1/G2	18	68	Ref.			Ref.		
G3	360	792	1.93	1.20–3.10	0.007	1.76	1.09–2.83	0.020
Neoadjuvant chemotherapy								
No	368	836	Ref.					
Yes	10	24	1.10	0.59–2.06	0.775			
Chemotherapy								
No	126	331	Ref.					
Yes	252	529	1.28	1.04–1.59	0.023			

DFS, disease-free survival; TO, Textbook Outcome; ASA, American Society of Anesthesiologists; BMI, body mass index; AJCC, American Joint Commission on Cancer; WHO, World Health Organization; HR, hazard ratio; 95% CI, 95% confidence interval; [#], T stage is classified by AJCC 8th and T4 contains T4a and T4b; [##], N stage is classified by AJCC 8th. N+ stages contain N1, N2, N3a and N3b.

Table S3 Univariate and multivariate Cox analysis of the clinicopathological factors for RFS

Clinical parameters	Event	Total	Univariable			Multivariable		
			HR	95% CI	P	HR	95% CI	P
Textbook outcome								
No	145	373	Ref			Ref		
Yes	140	487	0.72	0.57–0.91	0.005	0.76	0.60–0.96	0.022
Period								
2005–2007	8	20	Ref					
2008–2010	15	44	0.90	0.38–2.12	0.803			
2011–2013	101	240	1.25	0.61–2.56	0.551			
2014–2016	145	406	1.07	0.52–2.18	0.854			
2017–2018	16	150	0.47	0.20–1.10	0.082			
Hospital volume								
n≤50	116	289	Ref			Ref		
50<n≤100	57	233	0.53	0.39–0.73	<0.001	0.58	0.42–0.81	0.001
n>100	112	338	0.77	0.59–1.00	0.047	0.82	0.63–1.07	0.142
Age (year)								
≤65	156	478	Ref					
>65	129	382	1.08	0.86–1.37	0.498			
Sex								
Female	47	187	Ref			Ref		
Male	238	673	1.50	1.10–2.05	0.011	1.44	1.05–1.97	0.022
ASA score								
I–II	237	731	Ref					
III–V	33	82	1.40	0.97–2.01	0.072			
Unknown	15	47	0.96	0.57–1.61	0.866			
BMI (kg/m^2)								
<18.5	18	49	Ref					
18.5–25.0	196	547	0.94	0.58–1.52	0.792			
>25.0	51	176	0.73	0.42–1.24	0.244			
Unknown	20	88	0.51	0.27–0.96	0.038			
Tumor location								
Upper	150	445	Ref					
Middle	35	146	0.69	0.48–0.99	0.046			
Lower	81	220	1.11	0.84–1.45	0.469			
Overlapping	19	49	1.33	0.82–2.14	0.246			
Tumor size (cm)								
≤2	16	92	Ref					
>2 and ≤5	150	472	1.92	1.14–3.21	0.013			
>5	119	296	2.77	1.64–4.66	<0.001			
T stage (the AJCC 8th)#								
T1	3	57	Ref			Ref		
T2	15	81	4.13	1.19–14.25	0.025	3.69	1.07–12.76	0.039

Table S3 (*continued*)

Table S3 (*continued*)

Clinical parameters	Event	Total	Univariable			Multivariable		
			HR	95% CI	P	HR	95% CI	P
T3	41	164	5.58	1.73–18.00	0.004	4.88	1.51–15.80	0.008
T4	226	558	10.05	3.22–31.42	<0.001	8.42	2.68–26.43	<0.001
N stage (the AJCC 8th)##								
N0	53	236	Ref			Ref		
N+	232	624	1.90	1.41–2.55	<0.001	1.62	1.20–2.19	0.002
Grade (WHO 2010)								
G1/G2	15	68	Ref					
G3	270	792	1.71	1.02–2.87	0.044			
Neoadjuvant chemotherapy								
No	278	836	Ref					
Yes	7	24	0.99	0.47–2.09	0.973			
Chemotherapy								
No	89	331	Ref					
Yes	196	529	1.40	1.09–1.80	0.009			

RFS, recurrence-free survival; HR, hazard ratio; 95% CI, 95% confidence interval;

Table S4 Clinicopathologic description of G-NECs between medium- and high-volume centers

Variables	NECs (N=571)				
	50<n≤100	%	n>100	%	P
Total	233	40.8	338	59.2	
Tumor size (cm)					0.278
≤2	33	14.2	37	10.9	
>2 and ≤5	134	57.5	187	55.3	
>5	66	28.3	114	33.7	
T stage (the AJCC 8th)#					0.847
T1–T3	96	41.2	142	42.0	
T4	137	58.8	196	58.0	
N stage (the AJCC 8th)##					0.671
N0	57	24.5	88	26.0	
N+	176	75.5	250	74.0	

G-NEC, gastric neuroendocrine carcinoma; #, T stage is classified by AJCC 8th and T4 contains T4a and T4b. ##, N stage is classified by AJCC 8th. N+ stages contain N1, N2, N3a and N3b

Table S5 Risk factors related to TO

No. of risk factors	Total	TO				P
		No (n)	%	Yes (n)	%	
0	69	17	24.6	52	75.4	<0.001
1	332	120	36.1	212	63.9	
2	388	191	49.2	197	50.8	
3	71	45	63.4	26	36.6	

TO, Textbook Outcome.