

Clinicopathological Characteristics and Prognostic Factors of Patients with Gastric Cancer Accompanying Neuroendocrine Differentiation (NEDGC)

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Ya-Ping Wang 

Jun Hong

Jian Wang

Yi-Bing Bei

Han-Kun Hao

Lu-Chun Hua

Department of Surgery, Huashan Hospital, Fudan University, Shanghai 200040, People's Republic of China

Aim: Gastric carcinoma with neuroendocrine differentiation (NEDGC) is a relatively rare pathologic diagnosis in clinical practice, which has no specific guidelines or treatment recommendations yet. In this study, we aim to investigate the clinicopathological characteristics and prognostic factors of this disease.

Patients and Methods: We retrospectively analyzed clinicopathological data from a series of 82 NEDGC patients who underwent surgery for gastrectomy at Huashan Hospital Fudan University between January 2007 and December 2018. Furthermore, a series of 50 cases were used to analyze 3-year overall survival (OS).

Results: Ages of the patients ranged from 26 to 83 years (M:F, 4.8:1). The majority of patients suffered from some symptoms (97.6%), as the most common one was abdominal pain (48.8%). Most of the tumors were ≥ 5 cm (53.7%), in the lower part of the stomach (47.5%), and with advanced T (87.8% \geq T3) and N (67.1% \geq N1) stage. As to the neuroendocrine markers, Syn showed a slight advantage on sensitivity than CgA (79.3 and 75.6%, respectively). The 3-year OS was 54%. Advanced T stage (\geq T3) of the primary tumor, positive lymphovascular invasion (LVI), large tumor size (5.5cm), high neutrophil-to-lymphocyte ratio (NLR, 2.51), and low prealbumin level (173.87 mg/L) were associated with inferior OS based on the univariate analysis. Low preoperative hemoglobin level (113.87g/L), laparoscopic-assisted gastrectomy, and advanced N stage (N3) were three independent risk factors for 3-year OS of NEDGC patients in both univariate and multivariate analysis.

Conclusion: The TN staging system for gastric adenocarcinoma also has a prognostic value for NEDGC patients, while N3 stage works as an independent predictor of patients' survival. Since most of the NEDGC patients were in advanced stage, proper indications to perform operative laparoscopy should be selected.

Keywords: gastric cancer, neuroendocrine cell differentiation, prognosis, surgical treatment

Introduction

Gastric carcinoma with neuroendocrine differentiation (NEDGC) is a relatively rare pathologic diagnosis in clinical practice. According to the definition by the World Health Organization (WHO) in 2010,¹ NEDGC is a gastric neoplasm in which differentiated neuroendocrine (NE) cells are scattered as single cells or cell clusters among gastric carcinoma cells. NEDGC distinguishes itself from mixed adeno-neuroendocrine carcinoma (MANEC), which has been renamed to mixed neuroendocrine-non-

Correspondence: Lu-Chun Hua
Email 13391051806@189.cn

neuroendocrine neoplasms (MiNENs) in the WHO 2017 classification,^{2,3} by the volume of epithelial and NE cells components within the same tumor tissue.

However, since only ten years passed from the establishment and standardization of the NEDGC diagnostic system, little information of this disease is available. A few studies have shown the gradually increasing frequency recently, and in particular, revealed worse prognosis of NEDGC than those gastric cancer without NED.⁴⁻⁷ Therefore, is it inappropriate to classify and treat NEDGC just according to adenocarcinoma? Are specific guidelines or treatment recommendations essential for this tumor type?

In this study, we retrospectively studied 82 cases of NEDGC, which is a relatively large volume to our best knowledge, aimed to investigate the clinicopathological characteristics of NEDGC. Furthermore, in a series of 50 cases including, we analyzed prognostic factors of NEDGC after radical gastrectomy.

Patients and Methods

Patient Selection

We retrospectively analyzed clinicopathological data from patients diagnosed as NEDGC at Huashan Hospital Fudan University between January 2007 and December 2018. All the patients enrolled diagnosed pathologically after R0 resection with D2 lymphadenectomy and without the absence of

clinicopathological data. The exclusion criteria included pre-operative findings of distant metastasis or other original tumor, and adjuvant chemotherapy or radiotherapy. As to the prognosis-related analysis, two more criteria as followed included: (1) those with 3-year OS; (2) those with complete follow-up clinical data. The detailed flowchart of the cohort is shown in [Figure 1](#). This study was approved by Institutional Review Board of Huashan Hospital (HIRB; Shanghai, China) (No. KY2019-482). Written informed consent was obtained from all participants which included their clinicopathological data and survival outcomes. We confirmed that this report was conducted in accordance with the Declaration of Helsinki.

Diagnosis of NEDGC

The NEDGC diagnosis was confirmed by the general hematoxylin and eosin (H&E) histology, as well as by immunohistochemistry (IHC). More specifically, slices of each case were reviewed for both histological features of neuroendocrine neoplasms and IHC positivity for neuroendocrine markers, including synaptophysin (Syn) and chromogranin A (CgA). With the WHO 2010 classification¹ and expert consensus on gastrointestinal neuroendocrine oncology in China,⁸ NED was defined as the immunopositivity of one of the two neuroendocrine markers (Syn and CgA), and less than 30% volume within the area of the gastric adenocarcinoma. Ki67 index was evaluated in all cases for counting nuclear proliferation.

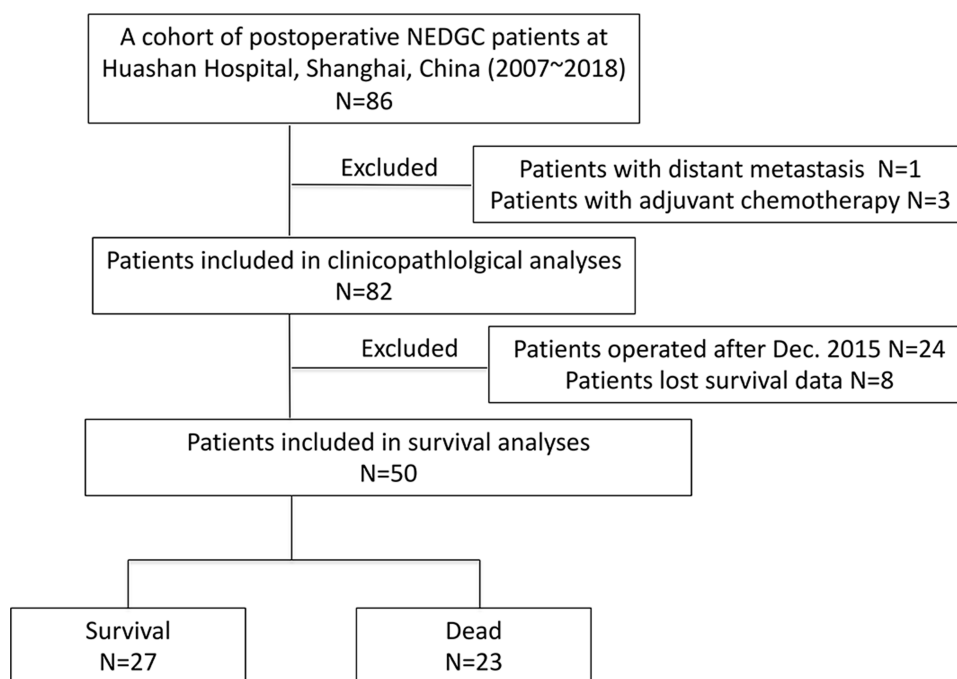


Figure 1 Flowchart of patients enrolled.

Treatment

The surgical method, including radical total gastrectomy and radical distal gastrectomy, was selected depending on the tumor location. Adjuvant chemotherapy based on 5-FU plus platinum-based drugs was taken for the patients with stage II or more advanced stage postoperatively.

Surgical resection margins R0 was defined as complete resection of the localized tumor, which was both confirmed during the operation by the surgeon and under macroscopic by the pathologists.

Clinicopathological Characteristics

Clinical data such as age, gender, body mass index (BMI), tumor location, tumor size, symptoms, complications, surgical treatment, operation time, preoperative blood biochemistry data, and follow-up information were recorded. Pathological data such as tumor TN stage, lymphovascular invasion (LVI), perineural invasion (PNI), expression of Syn and CgA, and Ki-67 index were also recorded.

Staging of the tumor was defined according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual for carcinoma of the stomach (8th Edn.).⁹ Tumor size was evaluated according to the maximum tumor dimension.

Survival Status

In the present study, we used 3-year OS as the primary outcome. OS was defined as the interval between date of surgery and date of last follow-up or death.

Patients were followed up every 3 months during the first 2 years and then every 6 months from 2 to 5 years, and then annually. Follow-up data were obtained by phone, outpatient visits, and our clinical database, and the date of the last follow-up was December 2019.

Statistical Analyses

Categorical and continuous clinicopathological characteristics of the cohort were firstly described using frequency (percentage) and median (range), respectively. We performed Log-rank tests to compare the 3-year OS rates across the T stages and N stages. The relationships between all variables and outcomes were quantified by univariate Cox regression analysis. Prognostic variables with $P < 0.05$ from univariate analyses were further included in a multivariate Cox proportional hazards analysis. The Statistical Package R, version 0.4.3 (R Foundation for Statistical Computing, Vienna,

Austria) was used for statistical analysis. $P < 0.05$ was considered statistically significant.

Results

Clinicopathological Characteristics

A total of 82 eligible patients with NEDGC diagnosed between 2007 and 2018 were included in the study. The clinicopathological characteristics of these patients are shown in Table 1. The median age was 62 years (range: 26–83 years), and 82.9% of the patients were male. The majority of patients suffered from some symptoms (97.6%), as the most common one was abdominal pain (48.8%). Other symptoms were abdominal distension (43.9%), acid reflux (24.4%), alimentary tract hemorrhage (24.4%), anemia (12.2%) and dysphagia (12.2%). No carcinoid syndrome was found in these cases. As to the other systemic disease complicated, hypertension is the most common one (26.8%), followed by chronic gastritis (11%) and diabetes (9.8%).

Tumor sizes ranged from 0.6 to 12 cm, with a median size was 5cm. Most of the tumors were ≥ 5 cm (44 cases, 53.7%). In terms of location, 29.3% of tumors were located in the upper, 23.2% in the middle, and 47.5% in the lower part of the stomach. According to AJCC 8th edition for gastric cancer, 12 patients were in stage I, 18 were in stage II, and 52 were in stage III. Although the majority of the patients were in advanced T stage (87.8% T3 or T4a) and had lymph nodes metastasis (67.1%), most of them without LVI and PNI (72% and 90.2%, respectively). As to the neuroendocrine markers, Syn showed a slight advantage on sensitivity than CgA (79.3% and 75.6%, respectively). High Ki-67 positive index also demonstrated in our study as 68 cases (82.9%) $\geq 30\%$, 35 cases (42.7%) $\geq 60\%$ including (Table 1).

Survival

As shown in Figure 1, 3-year OS was 54%, with the median survival time was 41 months. According to the univariate analysis, operation under laparoscopy, advanced T ($\geq T3$) or N (N3) stage of the primary tumor, positive LVI, large tumor size (5.5cm), high neutrophil-to-lymphocyte ratio (NLR, 2.51), low hemoglobin and prealbumin level (113.87g/L and 173.87mg/L, respectively) were associated with poor OS ($P < 0.05$; Tables 2 and 3; Figures 2–4). Among them, low preoperative hemoglobin level (HR 0.979; 95% CI: 0.958–1.000; $P = 0.046$), laparoscopic-assisted gastrectomy (HR 3.058; 95% CI: 1.169–8.000; $P = 0.023$), and N3 stage (HR 11.977; 95% CI: 3.025–47.420; $P < 0.001$) were three independent risk factors for OS in the multivariate analysis (Table 4).

Table I Clinicopathological Characteristics of NEDGC Patients

Category	Value	
Median age (range)	62	(26–83)
Gender		
Male	68	(82.9%)
Female	14	(17.1%)
BMI (kg/m²)		
<18.5	5	(6.1%)
18.5–23.99	51	(62.2%)
≥24	26	(31.7%)
Comorbidities		
Hypertension		
Yes	22	(26.8%)
No	60	(73.2%)
Diabetes		
Yes	8	(9.8%)
No	74	(90.2%)
Chronic gastritis		
Yes	9	(11.0%)
No	73	(89.0%)
Cardiac disease		
Yes	1	(1.2%)
No	81	(98.8%)
Chronic gastritis history		
Yes	9	(11.0%)
No	73	(89.0%)
Family history		
Yes	1	(1.2%)
No	81	(98.8%)
Drinking history		
Yes	12	(14.6%)
No	70	(85.4%)
Smoking history		
Yes	18	(22.0%)
No	64	(78.0%)
Presenting symptoms	80	(97.6%)
Weight loss		
Yes	23	(28.0%)
No	59	(72.0%)
Abdominal pain		
Yes	40	(48.8%)
No	42	(51.2%)
Abdominal distension		
Yes	36	(43.9%)
No	46	(56.1%)
Dysphagia		

(Continued)

Table I (Continued).

Category	Value	
Yes	10	(12.2%)
No	72	(87.8%)
Nausea		
Yes	5	(6.1%)
No	77	(93.9%)
Vomiting		
Yes	4	(4.9%)
No	78	(95.1%)
Acid reflux		
Yes	20	(24.4%)
No	62	(75.6%)
Anemia		
Yes	10	(12.2%)
No	72	(87.8%)
Alimentary tract hemorrhage		
Yes	20	(24.4%)
No	62	(75.6%)
Tumor location		
Upper	24	(29.3%)
Middle	19	(23.2%)
Lower	39	(47.5%)
Tumor size (cm)		
<2	6	(7.3%)
2–4.9	32	(39.0%)
≥5	44	(53.7%)
T stage (AJCC 8th Edn)		
T1/T2	10	(12.2%)
T3/T4a	72	(87.8%)
N stage (AJCC 8th Edn)		
N0 (0)	27	(32.9%)
N1 (1–2)	20	(24.4%)
N2 (3–6)	15	(18.3%)
N3 (≥7)	20	(24.4%)
Stage (AJCC 8th Edn)		
I	12	(14.6%)
II	18	(21.9%)
III	52	(63.4%)
LVI		
Yes	23	(28.0%)
No	59	(72.0%)
PNI		
Yes	8	(9.8%)
No	74	(90.2%)

(Continued)

Table 1 (Continued).

Category	Value	
CgA	+	62 (75.6%)
	-	20 (24.4%)
Syn	+	65 (79.3%)
	-	17 (20.7%)
Ki-67 positive index (%)	<30	14 (17.1%)
	30-59.9	33 (40.2%)
	≥60	35 (42.7%)

Abbreviations: LVI, lymphovascular invasion; PNI, perineural invasion; CgA, chromogranin A; Syn, synaptophysin.

Discussion

Gastric cancer is one of the most common malignancies worldwide, especially in the EAST. In recent years, a lot of progress has been made in surgery and adjuvant treatment, but the high mortality rate of this disease is still an unsolved problem, which attributed to detection too late.¹⁰ In this retrospective study, we regret to find that only 14.6% of cases were in stage I, and only one person diagnosed by physical examination with fibro gastro endoscope, who had no symptoms before. Since symptoms tend to show up in the course of diseases progressing, greater awareness should be raised to popularize routine physical examination, including endoscope. On the other hand, since the high level of morbidity and mortality of gastric cancer (with or without NED) in our country, it is a challenge to improve the techniques in tumor screening and treatment in this field.

As described previously, both CgA and Syn should be detected as diagnostic criteria of neuroendocrine. IHC markers CgA was reported as a nuclear protein with high specificity, while Syn was a transmembrane protein with high sensitivity.¹¹ Consistent with these studies is our finding. It reflects the importance of combined detection of these two markers in improving the sensitivity and specificity of NEDGC's diagnosis. However, although ki-67 is the most important prognostic and predictive biomarker in patients with g-NEN,^{12,13} its expression level in patients with NEDGC has no significant correlation with survival, which verified the rationality that classifies NEDGC as gastric adenocarcinoma than as g-NEN.

Table 2 Univariable (Categorical Variables) Cox Regression Analyses of OS

Category	n	3-y OS (%)	HR	95% CI	P
Gender	Male	39	53.85	0.95	0.35-2.55
	Female	11	54.55		
Hypertension complicated	Yes	13	38.46	0.60	0.25-1.41
	No	37	59.46		
Diabetes complicated	Yes	7	28.57	0.38	0.14-1.03
	No	43	58.14		
Chronic gastritis history	Yes	7	71.43	2.44	0.57-10.00
	No	43	51.16		
Smoking history	Yes	9	66.67	1.59	0.47-5.26
	No	41	51.22		
Drinking history	Yes	7	57.14	1.12	0.33-3.70
	No	43	53.49		
Surgical method	Laparotomy	39	64.10	3.49	1.47-8.27
	Laparoscopic	11	18.18		
Operation types	Total gastrectomy	21	47.62	0.74	0.33-1.68
	Distal gastrectomy	29	58.62		
Tumor location	Upper	13	46.15	Ref.	Ref.
	Middle	9	44.44		
	Lower	28	60.71		
T stage (AJCC 8th Edn)	T1/T2	12	91.67	10.22	1.37-75.98
	T3/T4a	38	42.11		
N stage (AJCC 8th Edn)	N0	14	78.57	Ref.	0.22-5.38
	N1	13	78.57		
	N2	11	45.45		
	N3	12	8.33		

(Continued)

Table 2 (Continued).

Category	n	3-y OS (%)	HR	95% CI	P
LVI					
Yes	15	33.33	0.40	0.17–0.91	0.029
No	35	62.86			
PNI					
Yes	5	20.00	0.38	0.13–1.12	0.081
No	45	57.78			
CgA					
Positive	39	53.85	0.92	0.27–3.21	0.902
Negative	11	54.55			
Syn					
Positive	40	50.00	0.48	0.19–1.22	0.123
Negative	10	70.00			

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; LVI, lymphovascular invasion; PNI, perineural invasion; CgA, chromogranin A; Syn, synaptophysin.

Furthermore, whether it is appropriate to use the prognostic TNM staging system for gastric adenocarcinoma in NEDGC patients is what we concerned about. The current study showed the trend of difference in survival among NEDGC patients at different T and N stage, and N3 was demonstrated as an independent risk factor for disease prognosis. As for no significant prognostic value of T stage and N0~N2 stage in the multivariate analysis, one important reason may be the limited cases. On the other hand, we did not include stage T4b or M1 cases since inappropriate for R0 resection, so we are unable to examine the prognostic implication of M stage. Nonetheless, our results do suggest that advanced T and N stage correlates to poor disease prognosis, and further analysis in this regard should be encouraged to reach a more accurate evaluation of prognosis.

Preoperative high NLR status had a negative prognostic effect in the patients with NEDGC is another interesting finding in the current study. As we have known, NLR represents an inexpensive marker of host inflammation. In the prior literature, a high NLR has been demonstrated to be prognostic in the advanced disease setting for a variety of solid tumors, including gastric cancer.^{14–17} Overall, our finding of this study is in keeping with the published literature, with a wealth of recent data of NEDGC suggesting that inflammation-based prognostic indicators such as the NLR are also

Table 3 Univariable (Continuous Variables) Cox Regression Analyses of OS

Category	Survival	Dead	HR	95% CI	P
Age	60.48(8.31)	62.83(12.40)	1.02	0.98–1.07	0.314
BMI (kg/m ²)	22.80(2.62)	22.63(2.93)	0.95	0.82–1.11	0.549
Operation time (min)	210.00[117.0]	184.00[80.0]	1.00	0.99–1.00	0.298
Blood losing volume (mL)	300.00 [225.0]	300.00[275.0]	1.00	1.00–1.00	0.230
Tumor size (cm)	4.26(2.28)	5.50(2.20)	1.18	1.01–1.39	0.038
Ki-67 positive index (%)	0.53(0.23)	0.47(0.22)	0.29	0.05–1.78	0.179
Preoperative test					
WBC	7.07(1.54)	6.26(1.87)	0.80	0.61–1.03	0.088
Neutrophils	0.60(0.10)	0.64(0.11)	38.59	0.57–2626.41	0.090
Lymphocytes	0.28(0.08)	0.25(0.10)	0.05	0.00–4.96	0.198
Monocytes	0.07[0.02]	0.07[0.03]	1.09	0.92–1.3	0.316
NLR (NeuLym)	2.00[1.33]	2.51[2.58]	1.19	1.03–1.39	0.019
LMR (Lym/ Mono)	3.99[1.79]	2.91[2.46]	0.96	0.81–1.14	0.663
Platelet	224.00[72.0]	202.00[80.5]	1.00	0.99–1.00	0.791
Hemoglobin	127.26(20.92)	113.87(22.49)	0.98	0.96–0.99	0.011
Albumin	38.89(3.77)	37.48(3.98)	0.92	0.83–1.01	0.094
Prealbumin	212.93(53.84)	173.87(61.26)	0.99	0.98–1.00	0.007
Blood glucose	5.20[0.95]	5.40[1.1]	0.76	0.52–1.12	0.166

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index.

generally associated with poor survival in NEDGC patients. Furthermore, since there is a lack of consensus regarding the most appropriate cut-off evaluation of the NLR, we treated it as a continuous variable. Univariate Cox regression test showed that the median value of the surviving group and the non-survivors was 2.51 and 2.00, respectively. It may be helpful to get a consensus regarding the definitions of “high” versus “low” NLR value of NEDGC patients in future studies.

As shown in [Figure 3](#), in the last decade, there was an increase not only in the incidence of NEDGC but also in the use of laparoscopic gastrectomy as the treatment. Since the first case of laparoscopic-assisted distal gastrectomy reported by Kitano et al in 1994,¹⁸ laparoscopic gastrectomy has been popularized with the expanding indication and decreasing complication in the past twenty years. Supported by a series of high-quality RCTs,^{19,20} laparoscopic gastrectomy for early gastric cancer is accepted widely. For locally advanced gastric cancer, laparoscopic gastrectomy with D2 dissection is still under debate, waiting for the long-term outcomes of relevant RCTs.^{21–23} According to our data, laparoscopic gastrectomy is an independent risk factor for 3-year OS in the same tumor staging baseline as in the open group. This phenomenon may due to

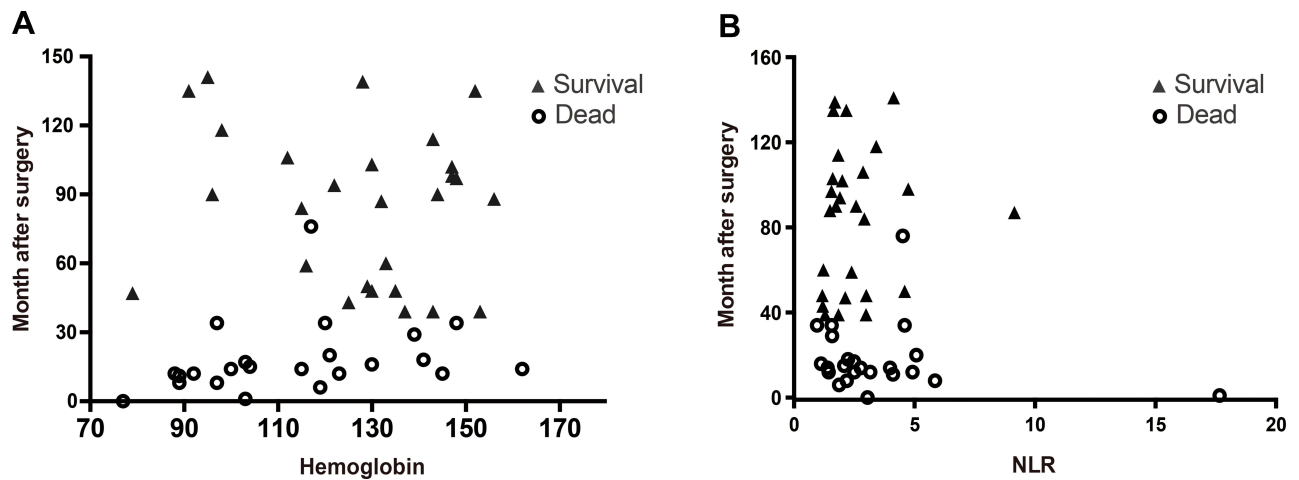


Figure 2 Survival analysis of NEDGC patients based on univariate Cox regression analysis. (A) Lower hemoglobin level was statistically associated with worse OS, since the median value of the surviving group and the non-survivors was 127.26 and 113.87g/L, respectively (HR 0.98; 95% CI: 0.96–0.99; $P=0.011$). (B) Higher neutrophil-to-lymphocyte ratio (NLR) was shown associated with worse OS, with the median value of the surviving group and the non-survivors was 2.51 and 2.00, respectively (HR 1.19; 95% CI: 1.03–1.39; $P=0.019$).

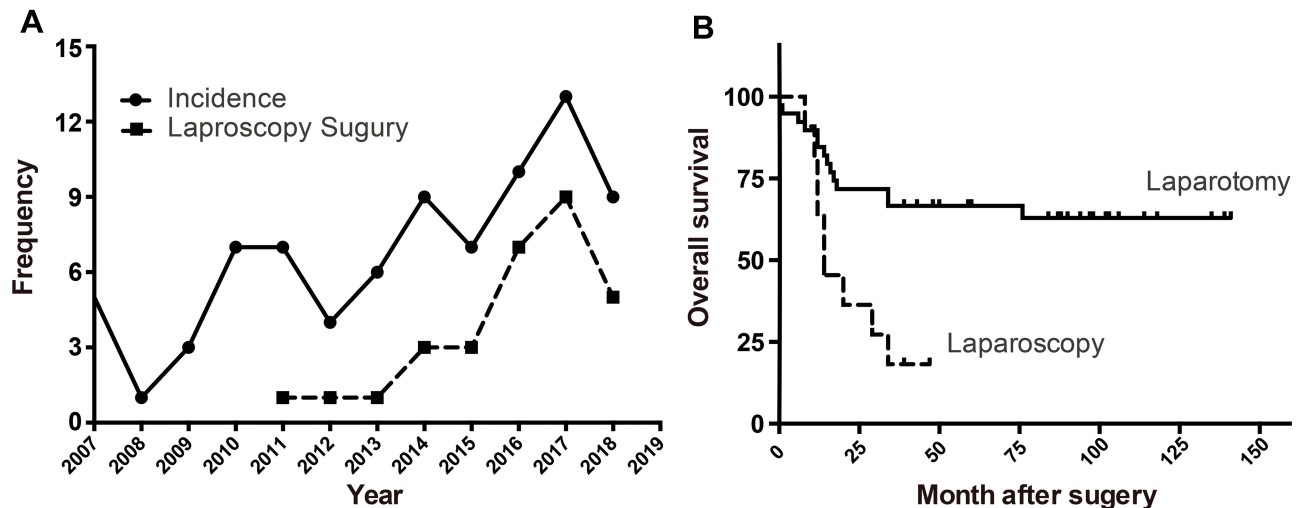


Figure 3 Incidence of NEDGC and cases of laparoscopic gastrectomy with Kaplan–Meier method estimated OS. (A) The number of newly diagnosed patients increased from 2007 to 2018, and the increased instances of laparoscopic gastrectomy in the past 5 years. (B) Survival analysis found significantly worse survival laparoscopic than laparotomy gastrectomy ($P=0.004$).

sample selection bias, that since laparoscopic gastrectomy is a new technique developed in recent years, the number of patients eligible for lap group is relatively small. Furthermore, regarding most of the NEDGC patients were advanced-stage cases, it is a caution for us to select proper indications to perform operative laparoscopy. How to make sure that the surgeons are qualified with skillful technique to accomplish the laparoscopic gastrectomy even with D2 dissection is also very important. Delightedly, bunds of organizations were conscious of this problem, and consensus on qualifying surgeons to perform laparoscopic gastrectomy was developed and promoted.^{24,25} So, it is not

the time to say “no” to perform laparoscopic gastrectomy on NEDGC patients. High-quality RCTs are necessary to explore this issue clearly in the near future. Still, proper indications selection and accumulation of laparoscopic gastrectomy skills are prerequisite, especially for the locally advanced NEDGC.

This study has several limitations. First, there is selection bias due to the nature of the single-center retrospective study. Second, due to the rare incidence, limited cases were qualified to analyze the prognosis, which may be affected by the disunity of chemotherapy postoperative either. Third, our study only included the resectable

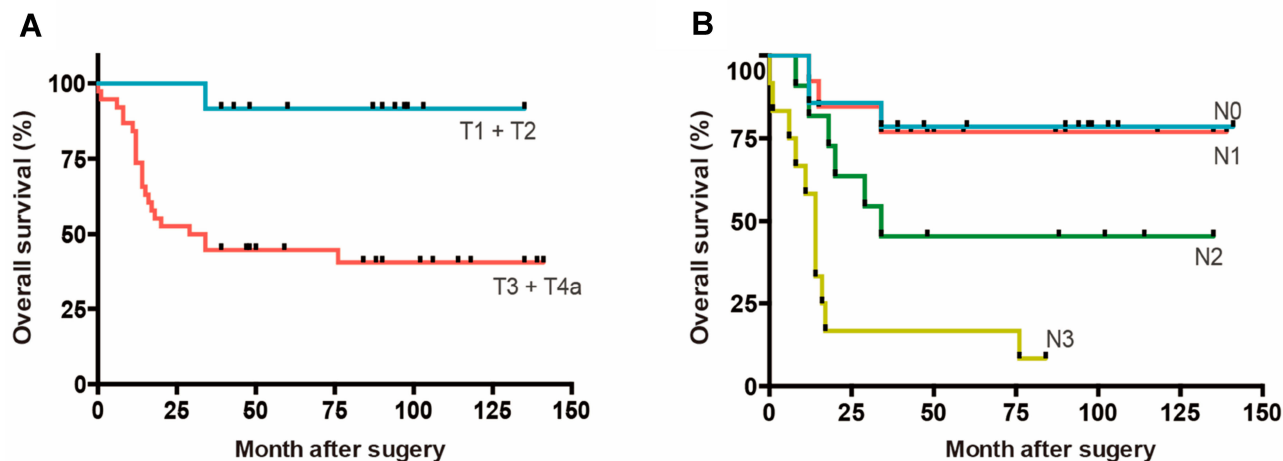


Figure 4 Kaplan–Meier method estimated OS in NEDGC patients grouped by (A) T stage of the primary tumor. Log rank analysis was carried out in stage T1+T2 and T3 +T4a cases, and the difference in OS was determined ($P=0.023$), (B) N stage of the primary tumor. Log rank analysis was carried out in different N stage cases. No significant difference was determined between stage N0, N1, and N2 patients ($P=0.921$ and 0.125 , respectively), while a significant difference was determined between stage N0 and N3 patients ($P=0.001$).

cases, which limited our ability to examine the prognostic implication of M stage in NEDGC patients. Last but not least, it is a data from Eastern countries, multicenter, prospective, large-sample analyses are needed for confirmation of our results.

In conclusion, the present study discovered that low pre-operative hemoglobin level, laparoscopic-assisted gastrectomy, and advanced N stage (N3) were three independent risk factors for OS of NEDGC patients. These findings indicate that the tumor staging system for gastric adenocarcinoma also helps to predict the prognosis of NEDGC. Since most of the NEDGC patients were in the advanced stage, proper indications to perform operative laparoscopy should be selected, and a better screening project for gastric cancer (with or without NED) is needed. Due to rare incidence, there is still a poor understanding of NEDGC as a clinical

entity. Further correct identification such as multicenter studies should be encouraged.

Consent for Publication

Patients provided written consent for the publication of their data.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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Table 4 Multivariable Cox Regression Analyses of OS

Category	P	HR	95% CI	
			Lower	Upper
Hb	0.046	0.979	0.958	1.000
Operation types (Laparotomy vs Laparoscopic)	0.023	3.058	1.169	8.000
N stage (AJCC 8th Edn)				
N0	0.001	Ref.		
N1	0.442	1.960	0.352	10.924
N2	0.050	4.250	0.998	18.099
N3	<0.001	11.977	3.025	47.420

Abbreviations: HR, hazard ratio; CI, confidence interval; Hb, hemoglobin.

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