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The impact of surgical resection on prognosis in gastric neuroendocrine tumors

Halit Batuhan Demir, Özgür Fırat

[1]*Department of General Surgery, Faculty of Medicine, Ege University, İzmir, Turkiye*

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ABSTRACT

Aims: This study aimed to investigate the pathological factors influencing prognosis in patients undergoing surgical resection for GNETs, in the context of the World Health Organization 2010 staging system.

Methods: This retrospective study included 27 patients who underwent surgical resection for GNETs diagnosis between 2001 and 2015. Patients were clinically categorized into four types based on GNET characteristics: type 1 tumors, which are typified by hypergastrinemia and develop on a background of atrophic gastritis; type 2 tumors, which are related with gastrinomas; type 3 tumors, which have low serum gastrin levels and no underlying mucosal pathology, and type 4, which are characterized by neuroendocrine carcinoma. Additionally, all patients were classified according to the TNM staging system.

Results: The median age of the patients was 56 years (range: 33-81), and most patients were identified as type I (55.6%), with subsequent groups being type IV (25.9%) and type III (18.5%). The majority of type I patients were classified as stage I, while the majority of type III patients were in stage IIA, and most type IV patients were in stage IIIB. Type III and type IV groups exhibited a higher rate of lymph node metastasis compared to type I group (Type I: 13.3% vs. Type II: 80.0% vs. Type IV: 57.1%, $p < 0.001$). The mortality rate was higher in the Type IV group compared to other groups (Type I: 0% vs. Type II: 20% vs. Type IV: 57.1%, $p<0.001$). The Ki-67 levels were higher in patients with lymph node metastasis than in those without.

Conclusion: Type III and IV GNETs are at a higher risk of lymph node metastasis and mortality. The Ki-67 value assessed through preoperative endoscopic biopsy may serve as a guide for deciding on the necessity of lymph node dissection.

Keywords: Classification, Ki-67, neuroendocrine tumor, stomach, prognosis

INTRODUCTION

Gastric neuroendocrine tumors (GNETs) originate from the excessive multiplication of enterochromaffin-like (ECL) cells, mainly situated in the fundus of the stomach. This proliferation is associated with an increase in plasma gastrin levels, resulting in various neoplastic transformations.[1] A study utilizing the Surveillance, Epidemiology, and End Results (SEER) database demonstrated that the age-adjusted annual incidences of GNETs were 0.30.[2] Results from the SEER database show that at the time of diagnosis, localized disease is identified in 53% of NET patients, while locoregional and distant metastatic diseases are found in 20% and 27% of patients, respectively.[3] The management and treatment of GNETs are of prognostic significance.

GNETs are associated with pronounced lymph node and liver metastases, and exhibits a high level of malignancy. However, the classification, pathology, and treatment strategies for GNETs are still largely unclear.[4] The low occurrence of GNETs continues to fuel debates regarding the appropriate treatment methods and the identification of the most effective treatment.[5] The World Health Organization (WHO) revised its classification scheme in 2010, segmenting it into three separate groups: type 1 tumors, which are typified by hypergastrinemia and develop on a background of atrophic gastritis; type 2 tumors, which are related with gastrinomas; type 3 tumors, which have low serum gastrin levels and no underlying mucosal pathology, and type 4, which are characterized by neuroendocrine carcinoma.[6] However, studies evaluating GNETs using this classification and comparing surgical outcomes are limited.

This study aimed to investigate the pathological factors influencing prognosis in patients undergoing surgical resection for GNETs, in the context of the WHO 2010 staging system.

METHODS

This retrospective study was conducted on patients diagnosed with GNETs at the Ege University Faculty of Medicine, Department of General Surgery, between January 2001 and December 2005. This study received approval from the Ege University Faculty of Medicine Ethics Committee and was

Corresponding Author: Halit Batuhan Demir, hb.demir@outlook.com

performed in accordance with relevant ethical guidelines, including the Declaration of Helsinki (2013 Brazil revision). Informed consent requirements were waived by the Ethics Committee due to the study's retrospective nature. This research is derived from the thesis titled 'Effect of surgical resection on prognosis in gastric neuroendocrine tumors".

The study retrospectively assessed 27 patients (≥18 years old) who were diagnosed with GNETs and underwent surgical resection. Patients under 18 years of age, those with a previous history of malignancy, and those with incomplete data were excluded from the study. The patients' demographic, clinical, and survival data were sourced from the hospital database, as well as pathology and radiology archives. Tumor size, lymph node status, lymphovascular invasion, and Ki-67 percentage were evaluated based on pathology findings. According to the WHO 2010 guidelines, GNETs were classified into four categories based on clinicopathological features: type I, type II, type III, and poorly differentiated neuroendocrine carcinomas (NECs, type IV).[6] In the pathology findings, the positivity of chromogranin, synaptophysin, and neuron-specific enolase were used as confirmatory evidence in the classification of GNETs. The overall survival time of the patients was monitored through the Death Notification System (https://obs.saglik.gov.tr). The death dates of deceased patients were recorded. The overall survival time for each patient was calculated in terms of months.

Statistical Analysis

The normality of numerical data was evaluated with the Kolmogorov-Smirnov test. Data were presented as mean±standard deviation or median (min-max) according to normal distribution. Depending on the normality of distribution for numerical variables, the Student's t-test and Mann-Whitney U test were used for comparisons between two groups, while the ANOVA and Kruskal-Wallis tests were employed for comparisons among more than two groups. Categorical variables are presented as numbers and percentages, and inter-group comparisons were conducted using Chi-square and Fisher's exact tests. Overall survival plots were created using Kaplan-Meier analysis. Values of $p<0.05$ were considered statistically significant. All data were analyzed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The median age of the patients was 56 years (range: 33-81), and 51.9% were male (n=14). Among the patients, 44% (n=12) had abdominal pain, 22.2% (n=6) experienced nonspecific symptoms, 18.5% (n=5) had dysphagia, and 14.8% (n=4) were afflicted with fatigue. The majority of the patients had tumors located in the corpus (37%), followed by the fundus (29.6%), antrum (18.5%), and cardia (14.8%). Based on GNETs classifications, most patients were identified as type I (55.6%), with subsequent groups being type IV (25.9%) and type III (18.5%). There were no cases identified as type II associated with Zollinger-Ellison syndrome (ZES) and multiple endocrine neoplasia 1 (MEN-1). It was found that total gastrectomy was performed on 11 patients (40.7%), subtotal gastrectomy on 9 patients (33.3%), and wedge resection on 7 patients. The median duration of hospitalization was 18.5 days (range: 6-35 days). The median follow-up period for the patients was 42 months (range: 1-171 months), and the mortality rate was 18.5% (n=5). No recurrence was observed in the remaining 22 patients throughout their follow-up period. The demographic and clinical characteristics of the patients were detailed in Table 1.

Table 1. The demographic and clinical characteristics of the patients with gastric neuroendocrine tumors

Variables	All population n=27
Age, years	56 (33-81)
Gender, n (%)	
Male	14 (51.9)
Female	13 (48.1)
Clinical symptoms, n (%)	
Abdominal pain	12 (44.0)
Dysphagia	5 (18.5)
Fatigue	4 (14.8)
Nonspecific symptoms	6 (22.2)
Tumor location, n (%)	
Corpus	10 (37.0)
Fundus	8 (29.6)
Antrum	5 (18.5)
Cardia	4 (14.8)
Tumor diameter, cm	2 (0.2-22)
TNM stage, n (%)	
I	10 (37.0)
IIA	7 (25.9)
IIB	2 (7.4)
IIIA	-
IIIB	7 (25.9)
IV	1 (3.8)
Type of GNETs, n (%)	
Type I	15 (55.6)
Type II	-
Type III	5 (18.5)
Type IV	7 (25.9)
Surgical procedures, n (%)	
Total gastrectomy	11 (40.7)
Subtotal gastrectomy	9 (33.3)
Wedge resection	7 (25.9)
Vascular invasion, n (%)	13 (48.1)
Lymph node metastasis, n (%)	10 (37.0)
Duration of hospitalization, days	19 (6-35)
Follow-up time, months	42 (1-171)
Mortality, n (%)	5 (18.5)

Categorical variables were shown as number percentages. Numerical variables are mean ± SD or median (min-max). TNM, tumor, node, and metastasis; GNETs, gastric neuroendocrine tumors

The distribution of age and gender was similar across GNET types. The majority of type I patients were classified as stage I, while the majority of type III patients were in stage IIA, and most type IV patients were in stage IIIB. The rates of vascular invasion were similar between type III and type IV groups. However, these groups exhibited a higher rate of vascular invasion compared to type I group (Type I: 20% vs. Type II: 80% vs. Type IV: 85.7%, $p < 0.001$). Type III and type IV groups exhibited a higher rate of lymph node metastasis

compared to type I group (Type I: 13.3% vs. Type II: 80.0% vs. Type IV: 57.1%, p < 0.001). The mortality rate was higher in the Type IV group compared to other groups (Type I: 0% vs. Type II: 20% vs. Type IV: 57.1%, p < 0.001) (Table 2) (Figure 1A). According to TNM stages, the mortality risk in patients with Stage III-IV was higher compared to other stages (Figure 1B). The deceased patients had a median tumor diameter of 5 cm, all exhibited vascular invasion, and the lymph node metastasis rate was at 80%.

Table 2. The distribution of TNM staging and prognostic findings according to GNET types

Variables	Type I n=15	Type III n=5	Type IV n=7	p
Age, years	53 (33-75)	56 (35-72)	58 (35-81)	0.845
Gender, n (%)				
Male	8 (53.3)	3 (60.0)	3 (42.9)	0.369
Female	7 (46.7)	2 (40.0)	4 (57.1)	
TNM stage, n (%)				
I	10 (66.7)	-	-	<0.001*
IIA	2 (13.3)	3 (60.0)	2 (28.6)	
IIB	-	2 (40.0)	-	
IIIB	3 (20.0)	-	4 (57.1)	
IV	-	-	1 (14.3)	
Surgical procedures, n (%)				
Total gastrectomy	5 (33.3)	2 (40.0)	4 (57.1)	<0.001*
Subtotal gastrectomy	3 (20.0)	3 (60.0)	3 (42.9)	
Wedge resection	7 (46.7)	-	-	
Vascular invasion, n (%)	3 (20.0)	4 (80.0)	6 (85.7)	<0.001*
Lymph node metastasis, n (%)	2 (13.3)	4 (80.0)	4 (57.1)	<0.001*
Duration of hospitalization days	16 (6-30)	19 (6-32)	20 (8-35)	0.126
Follow-up time, months	46 (24-171)	40 (8-164)	28 (1-118)	0.035*
Mortality, n (%)	-	1 (20.0)	4 (57.1)	<0.001*

Categorical variables were shown as number percentages. Numerical variables are mean ± SD or median (min-max). * p <0.05 shows statistical significance. TNM, tumor, node, and metastasis; LNM, gastric neuroendocrine tumors

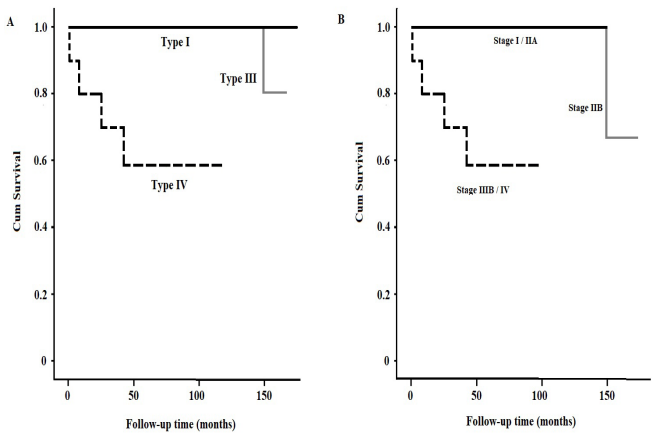

Figure 1. Survival findings of patients according to GNETs types (A) and TNM stages (B)

No significant relationship was found between Ki-67 and tumor diameter or vascular invasion (p>0.05). However, the Ki-67 levels were higher in patients with lymph node metastasis than in those without (Figure 2).

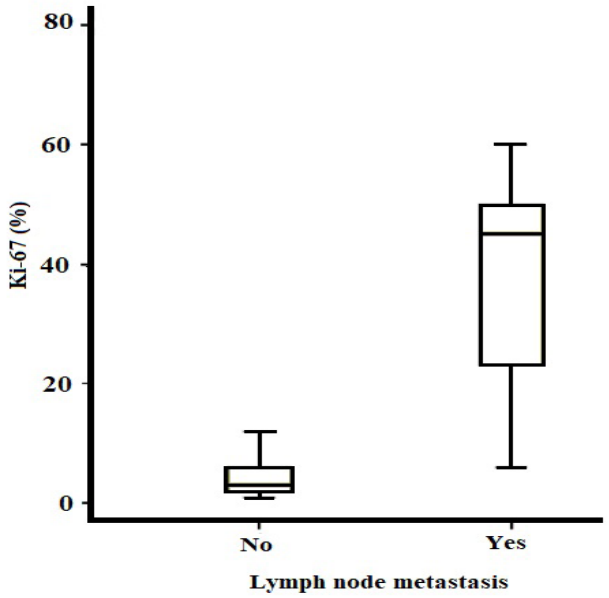

Figure 2. The distribution of Ki-67 levels according to the presence of lymph node metastasis

DISCUSSION

Globally, the TNM staging system is not widely accepted as the standard for neuroendocrine tumors. The classification embraced by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) corresponds to the classification related to carcinoids, which are designated as well-differentiated benign lesions by the WHO. In the classification accepted by the European Neuroendocrine Tumor Society (ENETS), carcinoids are defined as high-grade lesions.[7-10] However, either classification can be employed for gastric cancer cases. Type 1 and Type 2 GNETs often present as stage I or stage IIa, while Type III GNETs and NECs frequently appear as stage 2a, 2b, and stage 3b, and rarely as stage 4.[10] Similar to the literature, we found that the majority of type 1 patients were in stages I and IIA, while type 3 and NECs were in stages IIB, IIIB, and IV.

Although total gastrectomy is recommended for GNETs patients with tumor diameters below 2 cm, endoscopic excision has been shown to be safely applicable in Type 1 and 2 GNETs with lesions smaller than 1 cm.[11-13] In lesions with a tumor diameter greater than 1 cm, antrectomy can be performed along with the excision of accessible lesions.[14,15] Consistent with existing literature, these patients have undergone total gastrectomy, subtotal gastrectomy, and local excision procedures in our clinic. For patients who had deceased, the size of the tumor was above 3 cm. Moreover, during the median monitoring period of 42 months, there was no observed recurrence among the patients who survived.

Good prognostic factors for GNETs are their restriction to the mucosa and submucosa, the lack of vascular invasion, tumor diameters less than 1 cm, the absence of endocrine syndrome, and relationships with chronic atrophic gastritis (CAG) or MEN1-ZES.[16,17] The majority of type 1-CAG related GNETs are known to have a favorable prognosis.[11] NETs with aggressive characteristics demonstrate a poor prognosis due to their invasion past the muscularis propria, tumor diameters under 1 cm, vascular invasion, initial presentation with endocrine syndrome, elevated mitotic activity, and sporadic

occurrence.[14,18,19] NECs are frequently associated with a poor prognosis.[20] Also, it has been demonstrated that having a tumor diameter over 2 cm markedly increases the risk of metastasis in gastric NECs.[21] Previous studies have demonstrated that the rates of lymph node metastasis for GNETs type were 3-20% for type I, 12-30% for type II, 59-71% for type III, and 58-72% for NECs.[22-27] The present study found that the rates of lymph node metastasis were 13% for Type 1, 75% for Type 3, and 57% for NECs. It has been shown that primary tumor resection contributes to a better prognosis compared to non-surgical treatment in patients with Stage IV gastric NECs.[28] However, the mortality rate was higher in patients with NECs. This is consistent with patients with NECs having a worse prognosis.[20] Hence, patients with Type 3 and NECs should be closely monitored for 5 years compared to those with Type 1, due to the higher risk of a worse prognosis.[29,30] It has been proposed in various studies that employing endoscopic approaches like polypectomy, endoscopic mucosal resection, and endoscopic submucosal dissection (ESD) could be advantageous for excising small GNETs.[25,31,32] Additionally, it has been reported that in patients with submucosal gastric tumors who underwent wedge resection, no recurrence or metastasis was observed during a follow-up period of 61 months.[33] In this study, wedge resection was performed on about half of the patients with Type 1 GNETs, and there was no observation of recurrence or mortality throughout the follow-up.

Previous studies have demonstrated that the Ki-67 is an important tumor marker in predicting prognosis.[34,35] On the other hand, it has been shown that Ki-67 is significantly associated with a poor prognosis in early-stage gastric cancer but does not serve as a marker for poor prognosis in late-stage gastric cancer.[36] The differences between studies may be attributed to the clinical-demographic characteristics of the patients, such as age, stage, and tumor location, as well as the sample sizes of the studies. In this study, the lack of a significant relationship between Ki-67 levels and tumor diameter or vascular invasion suggests that while Ki-67 may serve as an indicator of proliferation, it does not directly correlate with these specific pathological features in GNETs. However, the higher Ki-67 levels in patients with lymph node metastasis indicate its potential utility as a prognostic marker for more aggressive disease courses. In the cases of GNETs, which are subject to discussions about lymph node dissection, evaluating the Ki-67 index via preoperative endoscopic biopsy could provide guidance on the necessity of performing lymph node dissection.

Limitations

This study has several limitations. The main limitation of the study was its single-center and retrospective design. Additionally, the small number of patients, the lack of standardization in the parameters evaluated by pathology varying over the years, and the uneven distribution of patients according to stages and GNETs types were other significant limitations. Lastly, the absence of GNETs associated with MEN1 and ZES precluded evaluations related to endocrine syndrome.

CONCLUSION

This study underscores the significant impact of surgical resection on the prognosis of patients with GNETs, utilizing the WHO 2010 staging system for classification. Our findings highlight the variability in outcomes based on tumor type, with type I GNETs showing a markedly better prognosis compared to the more aggressive type III and type IV tumors. The observed differences in mortality rates among GNET types, especially the significantly higher rate in type IV patients, point to the necessity of a tailored approach in the management of GNETs. The Ki-67 value assessed through preoperative endoscopic biopsy may serve as a guide for deciding on the necessity of lymph node dissection. Future studies with larger sample sizes and a multi-center approach are needed to validate these findings and further explore the role of Ki-67 and other markers in the prognostication and management of GNETs.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethical Committe of Ege University (Date: 24.12.2014, Decision No: 14.12-1T/58).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author.

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