Can Lymph Node Metastasis be Predicted in Gastroenteropancreatic Neuroendocrine Neoplasias?

Serhat Ocakli[1], Cengiz Ceylan[2], Firat Canlikarakaya[3], Abidin Goktas[4], Rumeysa Kankoc[5] and Serdar Gokay Terzioglu[4]

[1]*Department of General Surgery, Ankara Pursaklar State Hospital, Ankara, Turkiye*
[2]*Department of Gastrointestinal Surgery, Faculty of Medicine, Inonu University, Malatya, Turkiye*
[3]*Department of General Surgery, Tokat Niksar State Hospital, Tokat, Turkiye*
[4]*Department of General Surgery, Ankara City Hospital, Ankara, Turkiye*
[5]*Department of Pathology, Ankara City Hospital, Ankara, Turkiye*

ABSTRACT

Objective: To investigate the predictive factors influencing lymphatic metastasis in gastroenteropancreatic neuroendocrine neoplasm (GEP-NENs).

Study Design: Observational study.

Place and Duration of the Study: Department of General Surgery, Ankara City Hospital, Ankara, Turkiye, between the years 2019 and 2022.

Methodology: Patients who underwent surgery and were diagnosed with GEP-NEN based on final pathology between the study years were enrolled. Demographic information of the patients including age, gender, tumour location, and pathological characteristics (tumour size, grade, Ki-67 index, mitotic rate, total number of lymph nodes examined, pathological lymph nodes), inflammatory markers (White blood cell, lymphocyte, neutrophil, and monocyte counts, albumin levels, modified systemic inflammation score [mSIS], delta neutrophil index [DNI], neutrophil-lymphocyte ratio [NLR], and lymphocyte-monocyte ratio [LMR]) were retrieved from the patient database.

Results: One hundred and thirty-two patients were included. The median age was 51 (34-64) years, with 56.8% being male. GEP-NENs were most commonly found in the pancreas (43.2%) and appendix (22.7%). The median tumour size was 1.7 cm (0.7-3.5 cm), the mitotic rate was 1(1-2), and the Ki-67 Index was 2 (1-5). Grade I and II accounted for 91.6 % of cases. In multivariate analysis, independent predictive factors for pathological lymph node involvement were identified as small bowel tumour location ($p = 0.002$), tumour Grade III ($p = 0.008$), and tumour size ≥2 cm ($p = 0.017$).

Conclusion: This study identified tumour size, grade, and site of origin as independent risk factors for LN metastasis.

Key Words: *Neuroendocrine neoplasm, Lymph node metastasis, Gastrointestinal system*.

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INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NEN) is a general term used to describe neuroendocrine neoplasms that originate from the gastrointestinal system and pancreas. It encompasses all neuroendocrine neoplasms arising from these organs and represents the most common subgroup within the entire spectrum of neuroendocrine neoplasms.[1]

Correspondence to: Dr. Serhat Ocakli, Department of General Surgery, Ankara Pursaklar State Hospital, Ankara, Turkiye
E-mail: ocakliserhat@gmail.com
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The incidence of this condition is rising globally, with a higher prevalence in males and older individuals. In Europe, reported incidence lies between 1.33 and 2.33 per 100,000, while in the United States, it has increased roughly sixfold over the past 40 years, reaching 3.56 per 100,000.[2] While most cases are sporadic, some may also be associated with syndromes.

In GEP-NEN, the most important prognostic factors include tumour location, mitotic count, Ki-67 index, and the presence of metastasis.[3,4] Distant metastasis is a significant parameter that reduces overall survival. The prognostic impact of lymph node involvement in pancreatic and colorectal cancers has been the subject of proposed classifications, although no single system has yet gained widespread acceptance. However, it is well-established that positive lymph nodes are associated with advanced-stage and metastatic disease.[5] This study was designed to investigate the predictive factors influencing lymphatic metastasis in GEP-NEN.

METHODOLOGY

A total of 164 patients who underwent surgical procedures for gastrointestinal tumours and were diagnosed with neuroendocrine cancer based on final pathology, between the years 2019 and 2022 were enrolled in the Surgery Clinic of Ankara City Hospital, Turkiye. Demographic information of the patients including age and gender, tumour location, tumour pathological characteristics (tumour size, grade, Ki-67 index, mitotic rate, and total number of lymph nodes examined, and pathological lymph nodes), inflammatory markers (White blood cell count, lymphocyte count, neutrophil count, albumin levels, monocyte count, modified systemic inflammation score [mSIS], delta neutrophil index [DNI], neutrophil-lymphocyte ratio [NLR], and lymphocyte-monocyte ratio [LMR]) were retrieved from the patient database.

The patients were divided into two groups based on the presence or absence of pathological lymph nodes. All patients aged 18 years and older who were diagnosed with GEP-NEN in the preoperative and postoperative periods were included in the study. Patients with distant metastases were excluded from the study. This research obtained ethical clearance from the Institutional Review Board of the Ankara City Hospital, Turkiye, with an exemption from the requirement for informed consent (Date: 15.11.2023, Protocol Number: E1-23-4297).

The study's sample size was established through a power analysis using G-Power 3.1 software. A power (1-β) of 0.80 and a 95% confidence level were taken into account, culminating in a derived sample size of 30 subjects per cohort. Consequently, a minimal cumulative sample size of 60 subjects was ascertained for the collective cohorts. The evaluation of distribution normality was conducted utilising the Shapiro-Wilk's test. In instances where applicable, non-parametric assessments, notably the Mann-Whitney U test, were employed. Summary statistics encompassing median values and interquartile ranges (IQR) were documented for the variables under consideration. The optimal threshold values for tumour size, Ki-67 index, and mitotic rates were ascertained through the implementation of receiver operating characteristic (ROC) curve analysis. Categorical variables were examined using Chi-square analysis, and outcomes were presented in terms of frequencies and proportions. Subsequently, a prospective and carefully considered multivariate logistic regression analysis was carried out to examine the variables that exhibited statistical significance. The adequacy of fit of the logistic regression model was assessed using the Hosmer-Lemeshow test. Statistical significance was stipulated at a threshold of $p < 0.05$. The obtained data were analysed in the SPSS version 23.0 software package (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 164 patients were identified from the patient database, of whom 132 were included in the study. The population consisted of 75 (56.8%) males, with a median age of 51 (34-64) years. Neuroendocrine tumours were most commonly located in the gastrointestinal system in the pancreas (43.2%) and appendix (22.7%), while they were least frequent in the duodenum (3.0%) and rectum (0.8%). In the population, the median tumour size was 1.7 cm (0.7-3.5 cm), the mitotic rate was 1 (1-2), Ki-67 index was 2 (1-5), and Grade I and II accounted for 110 cases (91.6%). There were no patients with a mitotic count >20/2mm^2. Some images of the histologic and immunohistochemical examinations are provided in Figure 1. Lymph node metastasis was present in 33 (25%) patients based on pathological specimens (Table I).

In univariate analyses conducted for the estimation of pathological lymph node presence, statistical significance was observed with respect to tumour size ($p < 0.001$), mitotic rate ($p = 0.004$), Ki-67 index ($p < 0.001$), tumour grade ($p < 0.001$), and tumour location ($p = 0.005$). However, no statistically significant relationship was observed between the inflammatory parameters and the presence of pathological lymph nodes (Table II).

Table I: Demographic and tumour pathological characteristics.

Variables	Count (%)	Median (IQR)
Gender		
Male	75 (56.8%)	
Female	57 (43.2%)	
Age, years		51 (34-64)
Tumour size, cm		1.7 (0.7-3.5)
Mitotic rate		1 (1-2)
Ki-67 index, %		2 (1-5)
Grade		
I	66 (50.4%)	
II	54 (41.2%)	
III	11 (8.4%)	
Tumour location		
Appendix	30 (22.7%)	
Duodenum	4 (3.0%)	
Pancreas	57 (43.2%)	
Gastric	20 (15.2%)	
Small bowel	12 (9.1%)	
Colon	8 (6.1%)	
Rectum	1 (0.8%)	
LAP*		
Negative	99 (75.0%)	
Positive	33 (25.0%)	
Positive LAP*, n		0 (0-1)
Total LAP*, n		10 (5-15)

**LAP: Lymphadenopathy*

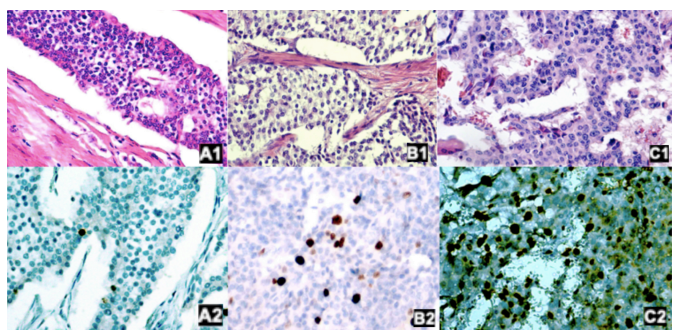

Figure 1: H&E* with ki-67 labelling of all grades (x40). H&E labelling, mitosis count 1/2mm^2, Grade I NEN of Colon (A1); immunohistochemistry, level of ki-67 2.4%, Grade I NEN of Colon (A2); H&E labelling, mitosis count 2/2mm^2, Grade II Gastric NEN (B1); Immunohistochemistry, level of Ki-67 6.6%, Grade II gastric NEN (B2); H&E labelling, mitosis count 4/2mm^2, Grade III pancreatic NEN (C1), immunohistochemistry, level of ki-67 23.5%, Grade III pancreatic NEN (C2).**
***Hematoxylin & Eosin*, ***Neuroendocrine Neoplasia*.**

Optimal cut-off points for tumour size, Ki-67 index, and mitotic rate were determined through ROC analysis (specifically, ≥2 cm, ≥4, and ≥2, respectively). In multivariate analysis, independent predictors for pathological lymph node involvement were identified as small bowel tumour location (p = 0.002), tumour grade III (p = 0.008), and tumour size ≥2 cm (p = 0.017, Table III).

DISCUSSION

The prognostic significance of lymph node metastasis, which affects treatment decisions, especially in early-stage tumours, is unclear. Although there are various recommendations for pancreatic and colorectal NENs, there is no common consensus. In this study, it was demonstrated that tumour location, tumour grade, and tumour size are independent risk factors for lymphatic metastasis in GEP-NEN.

Studies examining the relationship between lymph node metastasis and the calculated grade based on proliferative characteristics of neuroendocrine tumour (NET) are available.

In a study involving 2002 pancreatic NET patients, it was found that having a grade III tumour was an independent risk factor for lymph node metastasis.[6] Another study on pancreatic NET demonstrated that even in T1 tumours smaller than 2 cm, an increase in grade was associated with an elevated risk of lymph node metastasis.[7] However, in a study by Li *et al*. investigating LN metastases in gastric NET, grade was not identified as a risk factor.[8] This study revealed that the risk of lymph node metastasis increased approximately 19-fold in grade III tumours.

Ki-67 is one of the parameters determining tumour grade, and is a prognostic factor.[9] In this study, no statistically significant relationship was found between Ki-67 and lymph node metastasis. Studies in the literature investigating this relationship have yielded mixed results. In a study by Zheng *et al*. examining risk factors for lymph node metastasis in colorectal NENs, no relationship was observed between Ki-67 levels and LN metastasis.[10] However, in another study focusing on patients with ≤1.5 cm rectal NENs, it was shown that Ki-67 ≥3% increased the risk of LN metastasis up to six times.[11]

Another variable determining NEN grade is the mitotic count. In two studies investigating the relationship between mitotic count and LN metastasis in pancreatic and rectal NETs, no significant relationship was found between these two parameters.[12,13]

Although this study revealed a significant relationship between grade increase and the risk of LN metastasis, it was observed that the parameters constituting the grade, in line with the literature, did not have a stand-alone effect on LN metastasis.

Table II: Univariate analysis results.

Variables	LAP				p-value
	Negative Count (%)	Median (IQR)	Positive Count (%)	Median (IQR)	
Gender					
Male	55 (55.6%)		20 (60.6%)		0.612*
Female	44 (44.4%)		13 (39.4%)		
Age, years		50 (31-64)		55 (48- 66)	0.079+
Tumour size, cm		1.2 (0.6- 3)		2.7 (1.7- 5)	<0.001+
Mitotic rate		1 (1- 2)		2 (1- 4)	0.004+
Ki-67 index		2 (1- 4)		5 (3- 20)	<0.001+
Grade					
I	60 (60.6%)		6 (18.8%)		<0.001*
II	36 (36.4%)		18 (56.3%)		
III	3 (3.0%)		8 (25.0%)		
Tumour location					
Appendix	29 (29.3%)		1 (3.0%)		0.005*
Duodenum	3 (3.0%)		1 (3.0%)		
Pancreas	42 (42.4%)		15 (45.5%)		
Gastric	15 (15.2%)		5 (15.2%)		
Small bowel	5 (5.1%)		7 (21.2%)		
Colon	5 (5.1%)		3 (9.1%)		
Rectum	0 (0.0%)		1 (3.0%)		
Albumin		4.4 (4.1- 4.7)		4.3 (3.9- 4.6)	0.070+
WBC		7.29 (5.59- 10.01)		7.53 (6.28- 8.59)	0.956+
Neutrophil		4.61 (3.1- 7.46)		4.59 (3.41- 6.32)	0.775+
Lymphocyte		1.74 (1.41- 2.12)		1.79 (0.95- 2.34)	0.985+
Monosit		0.43 (0.33- 0.55)		0.42 (0.32- 0.56)	0.829+
Platelet		246 (207- 294)		242 (187- 323)	0.821+
DNI		0.1 (0.1- 0.1)		0.1 (0.1- 0.5)	0.479+
NLR		2.55 (1.76- 4.33)		2.57 (1.57- 4.81)	0.998+
LMR		4.07 (2.97- 5.4)		3.9 (2.97- 5.86)	0.902+
mSIS					
0	55 (55.6%)		17 (51.5%)		0.104*
1	38 (38.4%)		10 (30.3%)		
2	6 (6.1%)		6 (18.2%)		

**Pearson Chi-square test, +: Mann-Whitney U test*

Table III: Multivariate logistic regression analysis results.

Variables	Multivariate logistic regression		
	OR	95.0% CI	p-value
Tumour size ≥2 cm	3.477	1.251-9.667	0.017
Mitotic rate ≥2	1.611	0.508-5.107	0.418
Ki-67 index ≥4	1.198	0.349-4.111	0.774
Grade			
I	1		
II	3.554	0.840-15.026	0.085
III	19.346	2.163-173.058	0.008
Tumour location			
Appendix	1		
Duodenum	9.667	0.474-82.805	0.14
Pancreas	10.357	1.295-82.805	0.028
Gastric	9.667	1.034-90.412	0.047
Small bowel	40.600	4.070-405.039	0.002
Colorectal	17.400	1.495-202.470	0.023

One of the parameters influencing lymph node metastasis is the primary tumour location. In a study conducted by Martin *et al*., lymph node metastasis rates were reported as 65% for colon-origin tumours, 49% for stomach, 48% for rectum, 31% for appendix, and 24% for pancreas.[14] In this study, the lymph node metastasis rate was found to be 58% for small intestine-origin tumours, 44% for colorectal origin, 26% for pancreatic origin, 25% for gastroduodenal origin, and 3% for appendix-origin tumours. This difference was statistically significant. Multivariate analysis revealed that the primary tumour's location in the small intestine significantly increased the risk of lymph node metastasis up to 40 times ($p < 0.05$).

In a nomogram study aiming to predict lymph node metastasis in rectal NETs, tumour size ≥12 mm was reported as an independent risk factor for LN metastasis.[15] Another study examining LN metastasis in pancreatic NETs found tumour size >2 cm to be an independent risk factor.[16] However, in a study analysing 2,735 non-functioning pancreatic NET patients, unlike other studies, LN metastasis was detected in 24% of <1 cm grade I tumour, indicating that tumour size alone is not a reliable parameter.[17] In this study, multivariate analyses determined that tumour size >2 cm was an independent risk factor, increasing the risk of lymph node metastasis approximately 3.5 times ($p < 0.05$).

The relationship between cancer and inflammation was first proposed by Rudolf Virchow in 1863 and has regained importance in contemporary research. Although the mechanism is not yet fully understood, it is recognised that systemic inflammation plays a significant role in cancer pathogenesis and progression.[18,19] Therefore, in this study, the relationship between various inflammatory parameters and scores with lymph node metastases was investigated. However, no significant relationship was found. In a study examining resectable pancreatic NENs, an NLR ≤2.056 was found to increase the risk of lymph node metastasis by 6.7 times.[20] In this study, the lack of significance in this relationship was thought to be due to the fact that appendix NENs often present with acute appendicitis. The dominance of neutrophils in acute appendicitis was considered to have potentially rendered the statistical analysis of NLR and other inflammatory parameters meaningless.

CONCLUSION

Lymph node metastasis is a critical prognostic factor in GEP-NEN that significantly influences both treatment decisions and prognosis. Preoperative knowledge of lymph node status is therefore particularly important, especially for surgeons. This study has identified tumour size, grade, and location as independent risk factors for LN metastasis. The evaluation of these parameters was considered to be important in both, making treatment decisions and predicting prognosis. However, more extensive and prospective studies are needed to further investigate these aspects.

ETHICAL APPROVAL:

This research obtained ethical clearance from the Institutional Review Board, accompanied by an exemption from the requirement for informed consent (Date: 15.11.2023, Protocol Number: E1-23-4297).

PATIENTS' CONSENT:

This retrospective study was conducted with electronic records of patients. So, there was no need for further consent from the patients.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

SO: Collected and analysed the data, planned and designed the study, and drafted the manuscript.
CC: Planned and designed the study and performed the statistical analysis.
FC: Analysed the data and edited the manuscript.
AG: Collected and analysed the data.
RK: Histological and immunohistochemical examinations.
SGT: Reviewed and edited the manuscript.
All authors approved the final version of the manuscript to be published.

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