

Investigation of systemic treatment responses and prognostic factors in metastatic gastroenteropancreatic neuroendocrine carcinomas (GEP-NECs)

Alper Türkel¹, Duygu Ercan Uzundal², Fatih Gürler², İlknur Deliktaş Onur³,
Serkan Gülcü⁴, Ülkü Yalçıntaş Arslan³

¹Department of Medical Oncology, Eskişehir City Hospital, Eskişehir, Türkiye

²Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Gazi University, Ankara, Türkiye

³Department of Medical Oncology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, University of Health Sciences, Ankara, Türkiye

⁴Department of Medical Oncology, Ankara Etlik City Hospital, Ankara, Türkiye

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ABSTRACT

Aims: This study aimed to evaluate responses to first- and second-line treatments, survival outcomes, and potential factors affecting survival in patients with metastatic gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC).

Methods: This retrospective study included 42 patients with metastatic GEP-NEC from three centers. First and second-line chemotherapy regimens were examined. The median progression-free survival (mPFS1 and mPFS2) for first and second-line treatments and overall survival (mOS) were evaluated. The effects of CRP levels, LDH levels, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) on survival were investigated as potential prognostic factors.

Results: Median follow-up was 15 months (3-113). mPFS1 was 5 months (95% CI: 2.88-7.11) and mPFS2 was 2 months (95% CI: 1.67-2.32). The mOS was 15 months (95% CI: 10.90-19.09). Curative surgery patients had a 28-month mOS, and patients who could not undergo surgery had a mOS of 14 months ($p=0.010$). Patients with $NLR < 2.56$ had a longer mOS (22 months vs. 14 months, $p=0.019$) than those with $NLR \geq 2.56$. Multivariate analysis showed that lower NLR scores and Ki67 values were associated with longer mOS [HR: 0.38 (95% CI: 0.18-0.79), $p=0.010$ and HR: 0.41 (95% CI: 0.20-0.84), $p=0.015$]

Conclusion: Our study showed that higher NLR scores and Ki67 values significantly worsened mOS. Survival outcomes (OS, PFS1, and PFS2) aligned with the literature. NECs need new treatments and prognostic markers due to their poor prognosis, short survival times, and lack of standard guidelines.

Keywords: Extrapulmonary, neuroendocrine carcinoma, GEP-NEC, NLR

INTRODUCTION

Neuroendocrine carcinomas (NECs) are rare, high-grade, poorly differentiated, aggressive tumors with a poor prognosis.¹⁻³ Although approximately 90% of neuroendocrine carcinomas are of pulmonary origin, the most common site for extrapulmonary NECs is the gastroenteropancreatic (GEP) system. A study including 162,983 NEC cases found that only 9% of patients had extrapulmonary NECs, with 37.4% of these originating from the gastrointestinal tract.⁴ GEP-NECs are chemosensitive tumors; a combination of platinum and etoposide is the preferred chemotherapy regimen for treatment, similar to small-cell lung cancer.⁵⁻⁷ However, although most patients respond to first-line cytotoxic therapy, the response times are quite short [(median PFS: 4 months (3.4-4.6) 95% CI)].⁸ The current literature on second and later-line therapy is limited, and no established optimal treatment protocol exists. There are no randomized trials on this topic.

Additionally, a significant portion of patients cannot receive second-line therapy due to rapid clinical deterioration and/or declining ECOG performance status, and the best for these patients is supportive care.

Various studies have investigated some clinicopathological features and laboratory values that may affect the prognosis of neuroendocrine malignancies. These include Ki67 values,⁹ lactate dehydrogenase (LDH) levels,⁸ C-reactive protein (CRP) levels,¹⁰ white blood cell (WBC) and neutrophil count,¹¹ neutrophil-lymphocyte ratio (NLR),¹²⁻¹⁴ and platelet-lymphocyte ratio (PLR).¹⁵

This study investigated responses to first- and second-line treatments, survival outcomes, and potential factors affecting survival in patients with metastatic GEP-NEC.

Corresponding Author: Alper Türkel, turkelalperr@gmail.com



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METHODS

The study was carried out with the permission of the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 19.10.2023, Decision No: 2023-10/97). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective, multicenter study included 42 patients diagnosed with metastatic gastroenteropancreatic neuroendocrine carcinoma between December 2010 and December 2023. The inclusion criteria specified patients over 18 years of age with de novo or recurrent metastatic disease originating from the stomach, intestines, or pancreas who received at least two lines of chemotherapy and had complete access to their diagnostic and treatment records from the hospital registry system. Patients with pulmonary or unknown primary neuroendocrine carcinomas, those unable to receive chemotherapy, or those with incomplete diagnostic or treatment histories were excluded.

Data collected included demographic details such as age, sex, comorbidities, and smoking history, as well as clinicopathological features like tumor location, histological subtypes, Ki67 levels, sites of metastasis, first- and second-line chemotherapy regimens and cycles, and laboratory values, including WBC counts ($10^9/L$), neutrophil counts ($10^9/L$), CRP levels, LDH levels, platelet counts ($10^9/L$), NLR, and PLR.

In first-line treatment, platinum (cisplatin or carboplatin) plus etoposide treatment was preferred in the majority of patients according to treatment guidelines (although it was observed that different treatments were also preferred due to platinum ineligibility or low ECOG PS status), while in second-line, treatment selection was made according to the chemotherapy regimens which preferred more frequently by the centers where treatment decisions were made.

The patients' diagnosis, progression, and exitus or last follow-up dates were recorded. The time from initial diagnosis to progression under first-line treatment was defined as progression-free survival 1 (PFS1). The time from the date of progression after first-line therapy to progression under second-line treatment was defined as progression-free survival 2 (PFS2). The time from the date of initial diagnosis to the date of exitus or last follow-up was defined as overall survival (OS).

Statistical Analysis

Descriptive statistics were used to evaluate demographic and clinicopathological features. Survival analyses of median PFS1, median PFS2, and median OS were performed using the Kaplan-Meier method, and possible prognostic factors were compared using the log-rank test. OS was analyzed according to the time from the date of progression to the metastatic stage in patients to the date of last follow-up or exitus. The Cox regression method was used for multivariate analysis.

A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for personal computers, version 21.0.

RESULTS

Baseline Characteristics of Patients

Of the 42 patients included, 24 (57.1%) were male and 18 (42.9%) were female. The mean age of the patients was 57.7 (± 11.1). When primary tumor localizations were examined, 17 (40.5%) patients had pancreatic, 16 (38%) patients had gastric, and 9 (21.5%) patients had colorectal origin. In pathological assessment, 12 (28.6%) patients were diagnosed with small cell carcinoma, while 30 (71.4%) patients were diagnosed with large cell carcinoma. The median Ki67 value of the patients was 60% (21%-100%). At the initial diagnosis, 13 (31%) patients were eligible for upfront surgery with curative intent. Upon examination of metastatic sites, it was observed that the two most common metastatic locations were the liver and lymph nodes. All metastatic sites of the patients, along with their baseline characteristics, are detailed in [Table 1](#).

Table 1. Baseline characteristics of patients	
Age (years), ($\pm$ SD)	57.7 (± 11.1)
Sex (M/F), n	24/18
Smoking history, n (%)	
Active smoker	13 (31)
Non-smoker	20 (47.6)
Ex-smoker	9 (21.4)
ECOG performance status	
ECOG PS 0	11 (26.2)
ECOG PS 1	30 (71.5)
ECOG PS 2	1 (2.3)
Tumor localization	
Pancreatic	17 (40.5)
Gastric	16 (38)
Colorectal	9 (21.5)
Pathological subtype	
Small-cell	12 (28.6)
Large-cell	30 (71.4)
Ki67, %	
Mean value ($\pm$ SD)	59.6 (± 29.7)
Median value	60 (21-100)
Operation with curative intent	
Yes	13 (31)
No	29 (69)
Metastases sites	
Liver	32
Lymph nodes	24
Other organs	9

SD: Standard deviation, M: Male, F: Female, ECOG: Eastern Cooperative Oncology Group, PS: Performance Scale

Treatment Regimens

All patients (n=42) had received at least two lines of chemotherapy, and all patients (n=13) who were resectable at diagnosis and underwent curative intent surgery received

adjuvant chemotherapy. Of the 13 patients mentioned, 10 received cisplatin plus etoposide, 2 received carboplatin plus etoposide, and 1 received capecitabine plus temozolomide as adjuvant therapy. In the metastatic stages, when the first-line chemotherapy regimens of the patients were examined, 33 (78.5%) patients received platinum (cisplatin or carboplatin) plus etoposide combination. The median number of treatment cycles in the first-line setting was 6 (2-19). When the second-line chemotherapy regimens were examined, 10 (23.8%) patients received topotecan, and 10 (23.8%) patients received a capecitabine plus temozolomide combination. The median number of treatment cycles in the second-line setting was 3 (1-20). The other patients were treated with different treatment regimens. In addition, the platinum plus etoposide combination was preferred in both first-line and second-line treatment in three patients because they were considered platinum-sensitive. All first-line and second-line chemotherapy regimens are detailed in [Table 2](#).

Laboratory Assessment and NLR/PLR Scoring

Possible laboratory values and scores that may affect survival were evaluated as WBC count, neutrophil count, CRP levels, LDH levels, NLR, and PLR. The median WBC count was 7.2 ($10^9/L$) (2.3-16.9), and the median neutrophil count was 4.5 ($10^9/L$) (1.4-13). The median LDH level was 220 mg/dl (60-959). The median CRP level was 5.5 mg/dl (0-115). When NLR and PLR were examined, the median NLR was 2.56 (1.09-17.8), and the median PLR was 164 (55.6-334).

Survival Analyses

The median follow-up time was 15 months (range: 3-113 months). All patients received at least two lines of chemotherapy. Five patients received 3rd-line treatment, and two patients received 4th-line treatment. Median PFS1 was 5 months (95% CI: 2.88-7.11 months). Median PFS2 was 2 months (95% CI: 1.67-2.32 months). The median OS was 15 months (95% CI: 10.90-19.09 months).

Age, sex, Ki67 value, pathological subtype, operation status, NLR, PLR, CRP, and LDH levels were examined as possible factors affecting survival. The effect of each variable on PFS1, PFS2, and OS was analyzed separately.

In the univariate analysis, the median PFS1 for patients whose primary tumor was surgically removed with curative intent

at diagnosis was 10 months, whereas the median PFS1 for patients who could not undergo surgery was 4 months; this difference was statistically significant ($p=0.010$). No significant difference was found in PFS1 for any of the other factors examined ([Table 3](#)).

In the patient group with Ki67 $\leq 60\%$, the median PFS2 was 6 months, whereas in the patient group with Ki67 $>60\%$, the median PFS2 was 2 months; this difference was statistically significant ($p=0.004$) ([Figure 1](#)). In the group with LDH ≤ 220 mg/dl, the median PFS2 was 3 months, whereas in the group with LDH >220 mg/dl, the median PFS2 was 2 months; this difference was statistically significant ($p=0.043$). No significant difference was found in PFS2 for any of the other factors examined ([Table 3](#)).

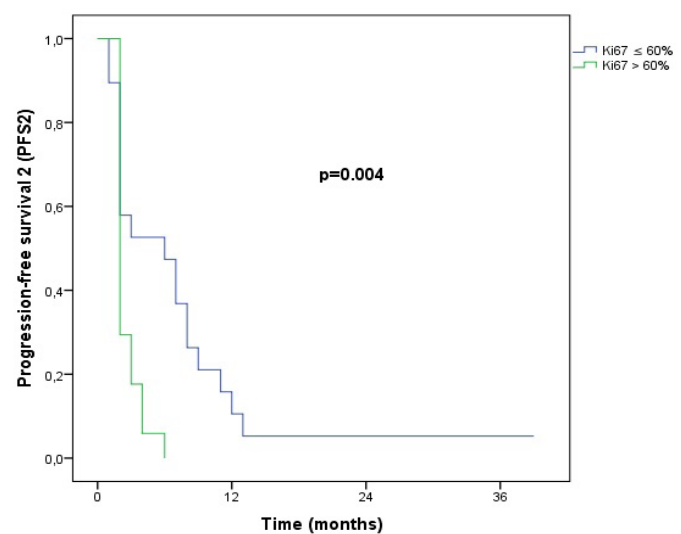


Figure 1. Kaplan-Meier curve for progression-free survival 2 according to Ki67 level

In the patient group whose primary tumor was surgically removed with curative intent, the median OS was 28 months. In contrast, the median OS was 14 months in the group that could not, and a significant difference was found between the two groups ($p=0.010$). In the patient group with NLR <2.56 , the median OS was 22 months, while in the group with NLR ≥ 2.56 , the median OS was 14 months, and a significant difference was found between the two groups ($p=0.019$) ([Figure 2](#), [Table 3](#)).

Table 2. Patients' 1st-line and 2nd-line treatment regimens

1 st -line regimens	Patients (n)	2 nd -line regimens	Patients (n)
Cisplatin plus etoposide	25	Topotecan	10
Carboplatin plus etoposide	8	Capesitabine plus temozolomide	10
Capesitabine plus temozolomide	7	Cisplatin plus etoposide	9
FOLFIRI	1	FOLFIRI	7
DCF	1	Carboplatin plus etoposide	3
Total	42	Cisplatin plus docetaxel	1
		FOLFOX	1
		Irinotecan	1
		Total	42

FOLFIRI: Folinic acid, 5-fluorouracil, and irinotecan, DCF: Docetaxel, cisplatin, and 5-fluorouracil, FOLFOX: Folinic acid, 5-fluorouracil, and oxaliplatin

Table 3. Univariate analysis of possible prognostic factors for survival

	Median PFS1 (95% CI)	p-value	Median PFS2 (95% CI)	p-value	Median OS (95% CI)	p-value
Age (years)						
≤58	4.0 (2.27-5.72)	0.248	2.0 (1.16-2.83)	0.730	15.0 (9.08-2.091)	0.456
>58	5.0 (2.80-7.19)		2.0 (1.59-2.40)		17.0 (8.23-25.76)	
Sex						
Male	5.0 (2.60-7.40)	0.785	2.0 (1.62-2.37)	0.682	14.0 (10.39-17.60)	0.440
Female	4.0 (2.61-5.38)		2.0 (0.95-3.04)		24.0 (6.48-41.51)	
Ki67 (%)						
≤60	6.0 (3.44-8.55)	0.588	6.0 (0.66-11.3)	0.004*	22.0 (8.43-35.56)	0.052
>60	5.0 (3.92-6.07)		2.0 (0.90-4.25)		13.0 (10.13-15.86)	
Pathological assessment						
Small-cell	4.0 (2.30-5.69)	0.425	2.0 (1.65-2.32)	0.611	13.0 (6.21-19.79)	0.707
Large-cell	5.0 (2.85-7.14)		2.0 (1.28-2.71)		17.0 (8.34-25.65)	
Operation at diagnosis						
Yes	10.0 (2.95-17.04)	0.010*	2.0 (1.69-2.34)	0.122	14.0 (8.87-19.12)	0.010*
No	4.0 (2.82-5.17)		2.0 (1.59-2.40)		28.0 (16.36-39.63)	
NLR						
<2.56	7.0 (4.07-9.92)	0.240	3.0 (0.38-5.61)	0.184	22.0 (6.33-37.66)	0.019*
≥2.56	4.0 (3.44-4.55)		2.0 (1.62-2.37)		14.0 (8.77-19.22)	
PLR						
<164	5.0 (2.80-7.19)	0.453	2.0 (1.55-2.44)	0.460	14.0 (7.42-20.57)	0.949
≥164	5.0 (3.07-6.92)		2.0 (1.07-2.92)		18.0 (10.38-25.61)	
CRP (mg/dl)						
≤5	5.0 (2.75-7.24)	0.907	2.0 (1.48-2.51)	0.818	13.0 (6.42-19.57)	0.661
>5	5.0 (0.51-9.48)		2.0 (1.62-2.34)		21.0 (13.97-28.02)	
LDH (mg/dl)						
≤220	6.0 (3.03-8.96)	0.789	3.0 (1.12-6.90)	0.043*	21.0 (16.15-25.84)	0.062
>220	5.0 (3.54-6.45)		2.0 (1.32-2.55)		13.0 (8.63-17.36)	
*: p<0.05, PFS1: Progression-free survival (1 st -line), PFS2: Progression-free survival (2 nd -line), OS: Overall survival, CI: Confidence interval, NLR: Neutrophil-lymphocyte ratio, CRP: C-reactive protein, LDH: Lactate dehydrogenase						

*: p<0.05, PFS1: Progression-free survival (1st-line), PFS2: Progression-free survival (2nd-line), OS: Overall survival, CI: Confidence interval, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, CRP: C-reactive protein, LDH: Lactate dehydrogenase

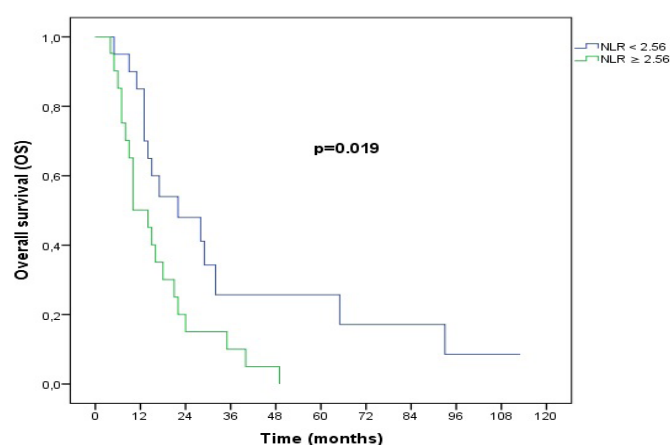


Figure 2. Kaplan-Meier curve for OS according to NLR

OS: Overall survival, NLR: Neutrophil-lymphocyte ratio

Multivariate analysis was performed to investigate the effects of curative intent surgery, Ki67 value, NLR, and LDH levels on median OS, which were identified as potential prognostic factors in the univariate analysis. As a result of the analysis, curative intent surgery and LDH levels, which were identified as significant prognostic factors in univariate analysis, lost

significance. However, a lower NLR was associated with longer median OS [HR: 0.38 (95% CI: 0.18-0.79), p=0.010]. Similarly, lower Ki-67 values were significantly associated with longer median OS [HR: 0.41 (95% CI: 0.20-0.84), p=0.015] (Table 4).

Table 4. Cox regression model for predicting the independent factors for median overall survival

	HR (95% CI)	p-value
Operation with curative intent		
No	Ref	
Yes	1.893 (0.798-4.492)	0.148
NLR		
≥2.56	Ref	
<2.56	0.388 (0.189-0.794)	0.010*
Ki67 (%)		
>60	Ref	
≤60	0.411 (0.201-0.841)	0.015*
LDH (mg/dl)		
≤220	Ref	
>220	1.048 (0.418-2.630)	0.920

HR: Hazard ratio, NLR: Neutrophil-lymphocyte ratio, LDH: Lactate dehydrogenase, *: p<0.05

DISCUSSION

NECs are rare, aggressive malignancies with a poor prognosis. The first-line treatment for NECs is platinum plus etoposide therapy.⁵ However, there is no consensus yet on second-line treatment. There is also no randomized study on the second-line treatment of GEP-NECs. In our study, we aimed to investigate the effectiveness of first-line and second-line therapies in patients with GEP-NECs.

When examining similar studies, Yamaguchi et al.'s¹⁶ retrospective study, which included 258 patients diagnosed with gastrointestinal system NECs, aimed to compare the effectiveness of irinotecan plus etoposide and cisplatin plus etoposide regimens, as well as to investigate their effects according to tumor localization. The median OS in all patients was 11.5 months, with median PFS1 ranging from 3.7 to 5.4 months and PFS2 ranging from 1.6 to 2.4 months, depending on the treatment regimen and tumor localization. As a result, it was noted that no clear difference was found between the two treatment regimens; however, larger studies were deemed necessary to determine whether different treatment options could be preferred based on tumor localization in treatment selection. The survival results of this study were similar to the results of our study. Yoon et al.'s¹⁷ study, including 64 patients diagnosed with GEP-NEC, investigated the effectiveness of cisplatin plus etoposide treatment. The PFS was determined to be 3.5 months (range, 3.7-5.3) in the entire patient group. In the study by Heetfeld et al.,¹⁸ including 167 patients with GEP-NECs, the median OS was 16.4 months (95% CI, 13.4-19.5 months), the median PFS1 was 5 months (95% CI, 4.0-6.1 months), and the median PFS2 was 2.98 months (95% CI, 2.56-3.41 months). The survival outcomes of these studies were similar to our study.

In neuroendocrine malignancies, studies have been conducted on factors and various scoring systems that may affect treatment efficacy and prognosis. The most frequently studied markers in this subject are inflammatory markers, including WBC count, neutrophil count, CRP, high-sensitivity CRP, LDH, and aspartate aminotransferase (AST).^{11,19} In addition, the prognostic value of scores such as NLR and PLR, which are derived by combining various laboratory values with these inflammatory markers, has been the subject of numerous studies.^{12,20,21} In these studies, results showed that increased WBC and neutrophil counts, as well as high NLR and PLR scores, are poor prognostic indicators. In our study, we found that increased NLR scores were associated with worse overall survival. The median NLR value in our study was consistent with the values reported in the literature.^{22,23} Upon examining numerous studies and meta-analyses, the cut-off value of PLR was determined to be between 150 and 300,²⁴ and our median PLR value fell within this range. Hypothetically, the ability to distinguish between good and poor prognostic patients with these scores may also affect treatment strategies. Although there are multiple treatment options in second-line treatment, none of them has become standard treatment. Additionally, there is no randomized study directly comparing these treatment approaches with each other in the current literature.

Targeted therapies have begun to play an important role in almost all cancer types with the increase in tumor-agnostic

markers. It is recommended to investigate actionable molecular alterations in the progression of NECs after first-line treatment. The main ones are pembrolizumab²⁵ and dostarlimab²⁶ in tumors with mismatch-repair deficiency (dMMR) or high microsatellite instability (MSI-H), pembrolizumab²⁷ and nivolumab plus ipilimumab²⁸ in tumors with high tumor mutational burden (TMB-H; ≥ 10 mutations per megabase), although data are limited, and the combination of dabrafenib plus trametinib in the presence of BRAF V600E mutation.²⁹ Additionally, less commonly, treatments targeting NTRK and RET fusions may also be considered.³⁰⁻³² However, the available data on these treatment options are limited, and actionable molecular alterations are not detected in the majority. In this patient group, the treatment decision can be challenging due to the lack of a standard treatment and limited treatment options. In the second-line treatment, similar to small-cell lung cancer treatment, platinum plus etoposide rechallenge treatment can be tried in cases of progression that develop more than 6 months after platinum plus etoposide treatment. However, in cases of progression that develop within 6 months, the current NCCN guidelines recommend capecitabine plus temozolomide, platinum-based chemotherapy plus irinotecan, FOLFOX, FOLFIRI, and FOLFIRINOX as treatment options. In a retrospective study conducted in Japan, which included 533 patients diagnosed with metastatic gastroenteropancreatic neuroendocrine neoplasm, it was shown that approximately half of the patients received treatments that were not recommended in the guidelines.³³ This situation has probably developed due to the lack of a standard treatment recommendation.

Ongoing clinical trials are investigating the efficacy of tarlatamab treatment, which has recently begun to gain traction in the treatment of small cell lung cancer, a type of NEC, as well as in the treatment of pulmonary and extrapulmonary neuroendocrine carcinoma.^{34,35} A significant portion of these studies investigates the efficacy of tarlatamab in second-line therapy in patients who have received platinum-based chemotherapy in first-line treatment. The fact that there is no satisfactory second-line treatment may change as a result of these studies. However, to our knowledge, there is no ongoing study specifically in GEP-NEC patients.

Limitations

Our study has several limitations, including the small number of patients and its retrospective, non-randomized nature. However, considering that a significant portion of patients with NEC can not receive second-line treatment due to the aggressive nature of the disease and limited treatment options, the number of patients in our study cannot be considered insignificant. Additionally, the fact that molecular tests, such as MSI or BRAF, were not performed for targeted therapies in any patient during the planning of first-line or second-line treatment may be considered another limitation. Furthermore, there are no randomized studies on this topic in the existing literature.

CONCLUSION

As a result, our study found that higher NLR scores and Ki67 values were significantly associated with worse median

OS. Survival outcomes were similar to those reported in the literature for both OS, PFS1, and PFS2. In the management of NECs, new treatment approaches and prognostic markers are needed due to the lack of standard treatment recommendations, poor prognosis, and short survival times.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 19.10.2023, Decision No: 2023-10/97).

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 Materials

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

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