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Research Article

Gastroenteropancreatic Neuroendocrine Tumors: Demographical, Clinicopathological, and Survival Data From Azerbaijan

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Abstract

Objectives: Neuroendocrine neoplasms consist of both well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas.[1] The study aims to report the demographic, clinical, pathological, and survival characteristics of patients with GEP-NETs.

Methods: Patients diagnosed with histologically confirmed GEP-NETs between 2018 and 2023 at the Liv Bona Dea International Hospital, Baku, Azerbaijan, were included in the study. Patient data, including clinical and histopathological characteristics, including age, gender, tumor location, clinical symptoms, type of treatment, ki-67 index, grade, and outcomes, were collected.

Results: A total of 51 patients were included in the study. The follow-up period of the patients varied from 3 to 74 months. The most frequent tumor location of the GEP-NETs was pancreas 19 (37%). Most of the tumors were non-functional (n=44, 85%), only a few showed functionality (n=7, 15%). Ki-67 index was high (>20%) in 6 (12%) of the patients. Eighteen of our patients had distant metastasis at the time of diagnosis (35%). The most common site for metastasis was liver (n=17, 33%).

Conclusion: To conclude, the high ki-67 index, functional tumor, high grade, and the presence of distant metastasis negatively affected the survival of GEP-NET patients in our setting.

Keywords: Gastroenteropancreatic neuroendocrine tumors, gastroenteropancreatic neuroendocrine neoplasms, survival

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Neuroendocrine neoplasms (NENs) originate from the neuroendocrine cell system, which can be found at a variety of locations with variable prognoses. They are a diverse group of malignancies with a neuronal phenotype and the ability to produce hormones and amines. NENs consist of both well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas.[1] Well-differentiated neuroendocrine neoplasms are called neuroendocrine tumors. The most common site for the NETs is the digestive system.[1] Almost half of the NETs originate from the gastrointestinal tract and pancreas and are called gastroenteropancreatic neuroendocrine neoplasms (GEP-NETs).[2] The incidence and prevalence of GEP-NETs have been rising annually, commonly due to increased

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awareness and improved diagnostic methods.[3] They are usually mild tumors with favorable outcomes. For the cases with poor outcomes, different studies show that several factors can affect the survival rates, such as age, gender, type of treatment, ki-67 index, distant metastasis status, grade, and location of the tumor.[1,2,4,5,6,7]

The aim of the study is to report the demographic, clinical, pathological, and survival characteristics of patients with GEP-NETs. To our knowledge, this is the first GEP-NET study in the literature which was reported from Azerbaijan.

Methods

Patients diagnosed with histologically confirmed GEP-NETs between 2018 and 2023 at the Liv Bona Dea International Hospital, Baku, Azerbaijan, were included in the study. Patient data, including clinical and histopathological characteristics, including age, gender, tumor location, clinical symptoms, type of treatment, ki-67 index, grade, and outcomes, were collected. NETs of the other organs and neuroendocrine carcinomas were excluded from the study. Tumor grading was determined according to WHO histopathological classification.[8] Overall survival (OS) was determined as the time from diagnosis to death in deceased patients and the last follow-up in living patients.

Statistical analysis was performed with Statistical Package for Social Sciences (SPSS) version 29.0 (SPSS Inc., Chicago, Il, USA). In univariate analysis, survival time was compared using the Log-rank test. Multivariate Cox regression analysis was applied to identify predictors of survival outcomes. The confidence interval (CI) was set as 95%, and a value less than 0.05 was adopted as statistically significant.

The study was approved by the Ethical Committee of the Liv Bona Dea International Hospital.

Results

A total of 51 patients were included in the study. During the follow-up period, 9 of the patients died. The median survival time could not be reached because of the short follow-up time and the small number of deaths in patients with well-differentiated GEP-NENs. The follow-up period of the patients varied from 3 to 74 months.

Of the 51 patients, 53 percent were females (n=27), and 47 percent were male (24). Female to male ratio was 1.13. Univariate analysis showed no significant difference in terms of survival in gender groups (p=0.485).

The median age of the patients in our study was 55, ranging from 26 to 84. No statistically significant difference was detected between age groups <50 and ≥50 (p=0.076).

The most frequent tumor location was pancreas 19 (37%), followed by stomach 12 (24%), small intestine 10 (20%), colon 2 (4%), and unknown primary 8 (16%). In general, the primary location of the tumor was found to have no statistically significant impact on OS (p=0.059).

Six (12%) of our patients had secondary malignancies at their diagnosis, 3 of them had colon adenocarcinoma and one of the patients had two additional malignancies lung adenocarcinoma and colon adenocarcinoma, 2 of them had endometrial carcinoma and one had non-Hodgkin lymphoma.

Regarding the functionality of GEP-NETs, most were non-functional (n=44, 85%), and only a few showed functionality (n=7, 15%). Functionality was found to have a significant effect on OS (p<0.001).

The most common first symptom among the cases was abdominal pain (n=36, 71%), followed by nausea (n=5, 10%), melena (n=2, 4%), weight loss (n=2, 4%), and diarrhea (n=1, 2%). Five of our cases were asymptomatic (10%) at the time of diagnosis.

Clinical T stage is another interesting data to be mentioned, 7 of the patients had T1 (14%), 6 of them had T2 (12%), 10 of them had T3 (20%), and 2 of the patients had a T4 tumor (2%), 26 of the tumors were not measured (51%). The mean tumor size was calculated as 35mm in our study.

Histopathological data demonstrated <3% ki-67 index in 25 patients (49%), 3-20% in 20 patients (39%), and >20% in 6 patients (12%), ranging from 1-80%. The difference between Ki=67 index groups was found to be statistically significant in terms of OS (p<0.001).

Two of the tumors could not be graded (4%), while 21 of them were grade 1 (41%), 20 were grade 2 (39%), and 8 were grade 3 (16%). The difference between tumor grades showed a significant difference in OS (p=0.011).

Twenty-three tumors were stained with both synaptophysin and chromogranin (45%), 20 of tumors were stained with synaptophysin but not with chromogranin (39%), 7 of the tumors were not stained with either synaptophysin or chromogranin (14%). Interesingly there wasn't any chromogranin positive but synaptophysin negative tumor in our study. No statistically significant differences were found between the different staining groups on OS (p=0.633).

Eighteen of our patients had distant metastasis at the time of diagnosis (35%). The most common site for metastasis was liver (n=17, 33%), followed by bone (n=5, 10%), kidney (n=1, 2%), pancreas (n=1, 2%). The absence of distant metastasis improved survival compared to the patients who had distant metastasis (p= 0.02).

Interestingly, 5 (10%) of our patients were misdiagnosed as adenocarcinoma (n=3) and neuroendocrine carcinoma (n=2).

For primary management 27 of our patients underwent surgery for curative intent (53%), while 23 of them received medical therapy (45%) and one patient refused any treatment. There was no significant difference between the treatment groups (p=0.9).

Of the 27 patients who underwent surgery and lymph node dissection, 12 of them had metastatic lymph nodes.

The most common medical treatment was Sandostatin LAR in our setting, with 16 patients receiving it. Other choices of chemotherapeutics were Lu-Dotatate (n=7), Capecitabine Temodal (n=2), Everolimus (n=1), Platin (n=1), and Etoposide (n=1). Four of the patients received Transarterial Radioembolization (TARE) as a locoregional therapy.

In addition to primary management, 3 of the patients who received curative surgery then underwent palliative surgery because of the progressive disease.

Twelve of the 27 patients who have undergone curative surgery developed metastasis after surgery, mean time from curative surgery to metastasis was 21 months.

Univariate and multivariate analyses of the factors predicting overall survival are shown in the Table 1 and 2 retrospectively.

Table 1. Univariate analysis of factors affecting overall survival

	Total, n=128	%	Exitus	Plog-rank for OS
Sex				0.485
Female	27	53	4	
Male	24	47	5	
Age				0.064
<50	13	25	0	
≥50	38	75	9	
Functionality				<0.001
Functional	7	15	6	
Non-functional	44	85	3	
Primary Tumor Location				0.059
Pancreas	19	37	4	
Stomach	12	24	4	
Small intestine	10	20	1	
Colon	2	4	0	
Unknown Primary	8	16	0	
Ki-67 index				<0.001
<3%	25	49	0	
3-20%	20	39	5	
>20%	6	12	4	
Grade				0.011
Grade 1	21	41	0	
Grade 2	20	39	2	
Grade 3	8	16	7	
Unable to grade	2	4	0	
Tumor staining				0.633
Synaptophysin + Chromogranin +	24	47	5	
Synaptophysin + Chromogranin -	20	39	3	
Synaptophysin - Chromogranin +	0	0	0	
Synaptophysin - Chromogranin -	7	14	1	
Presence of distant metastasis at diagnosis				0.02
Yes	18	35	7	
No	33	65	2	
Primary management				0.9
Surgery	27	53	4	
Medical	24	47	5	

Table 2. Multivariate analysis of factors affecting overall survival

Multivariate analysis	CI (95%)	p
Ki-67 index		0.024
<3%	0.696-51.623	0.103
3-20%	2.206-208	0.008
Functionality	0.052-0.834	0.027

Discussion

GEP-NETs are accounted as the second most commonly seen digestive tract malignancy in terms of prevalence.[9] In terms of prognosis, different studies showed multiple factors that affect the prognosis of GEP-NETs, but in general, the grade of the tumor, the presence of a distant metastasis at the time of diagnosis, and a high ki-67 index were found to significantly negatively affecting factors at many similar studies.[2,4,5,6,7] Our study showed that, in univariate analysis, the ki-67 index, functionality of the tumor, the grade, and the presence of distant metastasis were found to shorten the overall survival period. In multivariate analysis of the functionality of the tumor and Ki-67 index, were found statistically significant prognostic factors of OS.

The median age of the patients was similar in most of the studies, ranging from 51 to 57; in our study, the median age was also in that range (55).[4-7]

Some studies showed that age is a prognostic factor in terms of survival, but interestingly, our analysis did not reveal a statistically significant difference in OS between the patients who are less than 50 years old and those who are equal or more than 50 years old.[5,10]

The most common location is variable in different studies; Chinese and Arabian cohorts demonstrated data with pancreatic NETs to be the most common.[5,7] However, the Turkish cohort showed the stomach as the most common site.[10] The referral bias can cause these differences and make the racial variation in GEP-NET carcinogenesis possible.

The majority of GEP-NETs occur sporadically. However, they can also develop as a component of hereditary familial diseases, such as neurofibromatosis type 1, Von-Hippel Lindau syndrome, multiple endocrine neoplasia type 1 (MEN-1), and tuberous sclerosis.[11] None of the familial diseases were spotted in our patients. Our study also showed that 6 of the patients had secondary malignancies at the time of diagnosis and 3 of them had colon adenocarcinoma while one of the patients had lung and colon adenocarcinoma at the same time, this result may pioneer future research to understand if there is any relationship between adenocarcinoma and GEP-NETs.

Although most of the GEP-NETs are non-functional, functional tumors have a worse prognosis.[5] Our study also supports this data.

The most common symptom of the GEP-NETs is abdominal pain.[1] Thirty-six of the 51 patients were admitted to hospital because of abdominal pain.

The grading of the NENs was identified by the WHO. GEP-NENs are divided into six categories, and three of them are GEP tumors. All of the 3 NET categories are well differentiated but vary in mitotic rate and ki-67 index. Grade 1 tumors have a <2% mitotic rate and <3% ki-67 index, grade 2 tumors have a 2-20 mitotic rate and 3-20% ki-67 index, and grade 3 tumors have a >20 mitotic rate and >20% ki-67 index. The final grade is determined by whichever of the two proliferation indexes places the neoplasm in the higher-grade category.

In addition, there are two categories defining GEP neuroendocrine carcinomas (NECs): small-cell and large-cell NECs. They are both poorly differentiated with >20 mitotic rates and >20% ki-67 index. The last grade to be mentioned is mixed neuroendocrine neoplasms, which is a mixture of neuroendocrine and non-neuroendocrine neoplasms; they can be well or poorly differentiated, but in most cases, both parts are poorly differentiated.[8] In our setting, we had 7 patients who were diagnosed as NEC during the study period, but they were excluded to narrow the focus of the study. We have not seen mixed neuroendocrine neoplasm at our setting yet.

Although the main globally accepted grading system is the WHO's, China has its own grading system for the NENs, which keeps the grading system of the NENs under debate.[12]

The misdiagnosis of neuroendocrine tumors is a common occurrence even in highly sophisticated centers. A study by Carlie Sigel et al. showed us that 13% of the pancreatic neuroendocrine tumors at Memorial Sloan Kettering Cancer Center were initially misdiagnosed. We also saw approximately the same results in our setting, 5 of the 51 tumors (10%) were initially misdiagnosed, but after the clinician's suspicion of the tumors' behavior and diagnoses, the confirmation was requested, and the diagnoses were changed to NET.[13]

Treatment modalities include surgical and medical treatment. According to the latest guidelines by the European Society of Medical Oncology, the treatment options vary by the location of the tumor.[1] In general, the surgery is recommended for the grade 1 and 2 local or locoregional neuroendocrine tumors. Before any interventions, functional tumors must be treated medically. For metastatic tumors, surgery also plays a role after the correct determination of the tumor grading, primary site, and live metastasis involvement.

For high-grade GEP-NECs, the surgery should not be the first option to choose.[1]

Twenty-seven out of 51 patients received surgery for curative intent in our cohort, while only 3 received palliative

surgery after the primary management failed.

The medical therapy for NETs is variable and mainly divided into symptomatic treatment of the functional NETs and anti-proliferative treatment. None of the medical treatment options provide a cure, but rather the control of progression and symptoms.[11]

The main symptomatic therapy is somatostatin analogs (SSAs). Other options can be Theloristat Ethyl, peptide receptor radionuclide therapy, Everolimus (particularly for insulinoma), Diazoxide (particularly for insulinoma), and proton pump inhibitors (particularly for gastrinoma).[11]

For anti-proliferative therapy, there are broad options in 2 main subgroups: targeted drugs and systemic chemotherapeutics.

The most common targeted drug options are SSAs, IFN-a, Everolimus, and Sunitinib.

Systemic chemotherapeutics are recommended for advanced pancreatic NENs, G3 NETs, and NECs.[11,14]

Regarding medical treatment, Sandostatin was the most common treatment option in our setting, and for advanced tumors or in patients without response, Everolimus, Lu-Dotatate, Platin, and Etoposide were preferred options.[11,15]

Our study had some limitations. First of all, it was a retrospective study. Secondly, as it was done in a single center, the data provided does not represent the entire country or the region. In addition, the sample size was relatively smaller.

Conclusion

To conclude, our study reports data about the clinical, pathological, and survival characteristics of the GEP-NET patients from Azerbaijan. The high ki-67 index, functional tumor, high grade, and the presence of distant metastasis negatively affected the survival of GEP-NET patients in our setting. Since there was no data from our region regarding this disease, we hope the findings will be helpful for the physicians and be a valuable contribution to the GEP-NET literature.

Disclosures

Ethics Committee Approval: The study was approved by the Ethical Committee of the Liv Bona Dea International Hospital.

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Conflict of Interest: None declared.

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