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Two different characteristics and prognosis of grade 3 gastroenteropancreatic neuroendocrine tumors

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Abstract

Aim: Grade 3 gastroenteropancreatic neuroendocrine tumors (GEPNETs) are not a homogenous group, and this work aims at determining clinicopathologic, survival and prognostic differences in metastatic grade 3 GEPNETs with the help of Ki-67(mitotic index) and GA-68 PET CT/octreoscan.

Materials and Methods: Patients diagnosed with metastatic grade 3 GEPNETs were divided into two groups based on the Ki-67 cut-off point, 47, as Ki-67 low and high. Again, the patients were divided into two groups according to scan positivity, and all four groups were compared on the basis of clinicopathologic characteristics, survival and prognostic factors.

Results: Twenty-six patients were included in the study. The median overall survival in low group was 20 months and 10 months in high group (p=0.321). Lower Ki-67 scan positive group had longer overall survival than lower Ki-67 scan negative group (NR vs 3 months, respectively, p=0.067). In the high Ki-67 group, the median overall survival was longer in scan positive than negative group (10 vs 9, respectively, p=0.956).

Conclusion: The median overall survival was longer in patients with low Ki-67 levels compared to high Ki-67 levels. The best overall survival was in low Ki-67 and scan positive group.

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEPNETs) are classified according to Ki-67 proliferative index. Ki-67 index lower than or equal to 20% is classified as a grade1-2 and an index higher than 20% is classified as a grade 3 [1]. Grade 3 tumors are not a homogenous group [2]. The differentiation status is an important prognostic factor [3]. Grade 3 tumors include poorly and well-differentiated characteristic groups [4]. Recent publications showed that Grade 3 GEPNETs had different somatostatine receptor uptake and survival, according to Ki-67 proliferative index and morphology [5,6,7]. In a study, it was shown that differentiation status and Ki-67 levels correlate with chemotherapy sensitivities [8,9]. These factors could impact therapeutic decisions. In 2017, the WHO classification proposed a division of grade 3 tumors into two groups namely, poorly differentiated G3 NEC (grade 3 neuroendocrine carcinoma) and well differentiated G3 NETs for tumors arising pancreatic primary [10]. However, distinguishing these two categories is difficult because of the absence of well-defined histological criteria and differences in Ki-67 assessment [11]. Additional factors to predict behaviour of grade 3 gastroenteropancreatic tumors are needed. Somatostatin receptor (SSTR), most commonly the subtype 2 and 5 expressions, is high in well differentiated neuroendocrine tumors [12]. 68 Gallium and Indium 111 bind to somatostatin receptors (SSTRs) [13,14]. Poorly differentiated tumors more likely have lower somatostatin receptor expression, so it is expected not to be visualized by In 111 octreotide scan

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and Ga-68 PET CT scan [15]. We hypothesized that high 68Ga and In 111 uptake are associated with good differentiation..

We aimed at determining the clinicopathologic and prognostic differences between Ga-68 and octreoscan positive and negative groups in grade 3 gastroenteropancreatic tumors according to the Ki-67 prognostic index.

Materials and Methods

All patients diagnosed with metastatic grade 3 gastroenteropancreatic neuroendocrine tumor in Erciyes University Medical School were retrospectively reviewed. We included only patients that had previously had Ga-68 PET CT or In 111 octreotid scan (octretid scan) performed on them. Sample sizes couldn't be calculated because of the rarity of this population. We excluded patients diagnosed with adenoneuroendocrine carcinomas from the study.

Data collected from the hospital's patient records included patients' characteristics, primary tumor location, first line chemotherapy regimens given to them, Ki-67 levels, metastatic sites, number of metastatic sites, date of death.

We divided patients diagnosed with grade 3 gastroenteropancreatic neuroendocrine tumors into 2 groups based on the Ki-67 index. The cut-off points of Ki-67 determined as level 47 by ROC curve analyses (Area under the curve: 0.613 spesivity: 0.600 sensitivity: 0.688). The patients that had Ki-67 lower than level 47 were classified under the low Ki-67 group and those with Ki-67≥ 47 were catalogued into the high Ki-67group. In the Ga-68 PET CT and octreotid scan, imaging pathological uptake was accepted as scan positivity. Low and high Ki-67 groups were further divided into two groups according to Ga-68 PET CT/octreotid scan positivity. All groups were compared according to overall survival of each other. The primary end point of the study was overall survival according to Ki-67 level and scan positivity.

The present study was approved by the ethics committee of Erciyes University (29.01.2020 No: 2020/72).

Statistical analysis

Non-probability sampling method was used while collecting data. The median, min, max and frequencies were defined. Mann Whitney U tests were used for continuous variables and chi-square tests were used for categorical data. The Kaplan–Meier method and log-rank test were used to analyses survival. OS was defined as the time from diagnosis of grade 3 GEPNETs to death or last evaluation. ROC analyses were also used to determine a cut-off value for Ki-67 levels. A p value <0.05 was regarded as statistically significant. Statistical Package for Social Sciences 22.0 (SPSS Inc., Chicago, IL, USA) software was used in all statistical analyses.

Results

We included 26 patients diagnosed with grade 3 GEPNETs in our study. A 111 octreotide scan was performed on 6 patients (23%) and a Ga-68 PET CT scan was performed on 20 patients (77%). Eleven of the patients (42%) were in the low Ki-67 group and 15 of the patients (58%) were in the high Ki-67 group. Five (45%) of patients were scan-positive and 6 (55%) of patients were scan-negative in the low Ki-67 group. Nine (60%) of patients were scan-positive and 6 (40%) of patients were scan-negative in the high Ki-67 group.

In the scan-positive low Ki-67group, there were 3 (43%) males and 4 (57%) females, and in the scan-negative low Ki-67 group, there were 4 (100%) males only. In the scan-positive high Ki-67 group, there were 7 (78%) males and 2 (22%) females while in the scan-negative high Ki-67 group there were 2 (33%) males, 4 (67%) females.

In the scan-positive low Ki-67group, the primary sites were the small intestine in 1 (14%), colon in 1 (14%), stomach in 2 (29%), pancreas in 3 (43%) patients. On the other hand, in the scan-negative low Ki-67 group, primary sites were the stomach in 3 (75%), pancreas in 1 (25%) patients. In the scan-positive high Ki-67 group, the primary sites were stomach in 2 (22%), pancreas in 7 (78%) patients. Lastly, in the scan-negative high Ki-67 group, the primary sites were the stomach in 3 (50%), and the pancreas in 3 (50%) patients.

The number of the primary were resected patients were 4 (58%) in the scan-positive low Ki-67 group and 2 (50%) in the scan-negative low Ki-67 group; 3 (33%) in the scan-positive high Ki-67 group and 3 (50%) in scan negative high Ki-67 group.

The patients who had liver metastasis were 71% in the scan-positive low Ki-67 group, 75% in the scan-negative low Ki-67 group, 89% in the scan-positive high Ki-67 group, and 83% in the scan-negative high Ki-67 group.

The objective response rate to the first-line chemotherapy was 13% in the low Ki-67 group, and 47 % in the high Ki-67 group. All general characteristics are summarized in Table 1.

Overall survival

The median overall survival in the low Ki-67 group was 20 months and 10 (5.65-14.34) months in the high Ki-67group. This, however, did not reach a statistically significant level (p= 0.321). In the low Ki-67 group, the median overall survival of Ga-68 or In 111-positive patients had not yet reached a certain point in follow-up time, the median overall survival of negative patients was 3 (0.85-5.14) months (p=0.067).

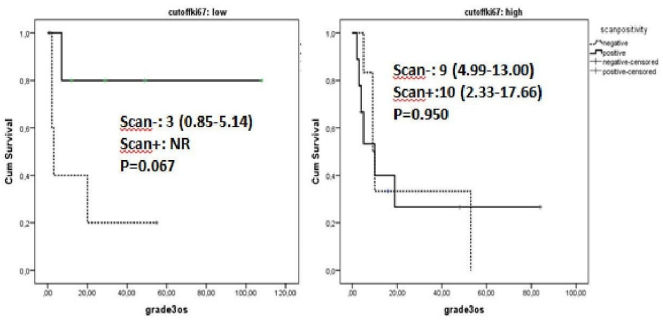

Figure 1. Overall survival of grade 3 gastroenteropancreatic neuroendocrine tumors in scan positive and negative group according to Ki-67 level.

Table 1. General characteristics.

Characteristics	Ki-67 low group (Ki-67<47) N=11, 42 %			Ki-67 high group (Ki-67≥47) N=15, %58		
	Scan positive (N=7, 64%)	Scan negative (N=4, 36%)	p	Scan positive (N=9, 60%)	Scan negative (N=6, 40%)	p
Age years, min-max	48 (33-60)	61 (54-64)	0.537	59 (30-70)	45 (18-65)	0.224
Gender						
Male	3 (43 %)	4 (100%)	0.242	7 (78%)	2 (33%)	0.136
Female	4 (57 %)	0		2 (22%)	4 (67%)	
Primary Site						
Small bowel	1 (14%)	0		0	0	
Colon	1 (14%)	0		0	0	
Stomach	2 (29%)	3 (75%)		2 (22)	3 (50%)	
Pancreas	3 (43%)	1 (25%)		7 (78)	3 (50%)	
Surgery						
Yes						
Curative	2 (29%)	0	1	1 (11%)	1 (17%)	1
Palliative	2 (29%)	2 (50%)		2 (22%)	2 (33%)	
No	3 (42%)	2 (50%)		6 (67%)	3 (50%)	
Metastatic site						
Liver	5 (71%)	3 (75%)	0.182	8 (89%)	5 (83%)	0.229
Lung	1 (14)%	3 (75%)	0.061	3 (33%)	0	1
Bone	3 (42%)	0	1	1 (11%)	0	
Others	1 (14)	1 (25%)		1 (11%)	1 (17%)	
Number of metastatic site						
1	5 (71%)	1 (25%)	0.242	6 (67%)	6 (100%) 0	0.229
2 and upper	2 (29%)	3 (75%)		3 (33%)	(0%)	
NSE						
High	4(58%)	1 (25%)	0.206	4 (44%)	3 (50%)	1
Not High	3 (42%)	1 (25%)		4 (44%)	2 (33%)	
Not available	0	2 (50%)		1 (12%)	1 (17%)	
Chemotherapy						
Platinum-Etoposide	1 (14%)	0		6 (75%)	5 (83%)	
5FU+Streptozosin	2 (29%)	0		0	1 (17%)	
CAPTEM	3 (43%)	2 (50%)		2 (25%)	0	
No chemotherapy	1 (14%)	2 (50%)		1	0	
Best Response to first line						
Chemotherapy						
PR/CR	1(17%)	0		4 (57%)	3 (50%)	
SD	3 (50%)	1 (50%)		1 (14%)	1 (17%)	
PD	2 (33%)	1 (50%)		2 (29%)	2 (33%)	
Previous PRRT						
Yes	5 (71%)	0		3 (33%)	0	
No	2 (29%)	4 (100%)		6 (67%)	6 (100%)	
Somatostatin analougues						
Yes	5 (71%)	0		2 (22%)	0	
No	2 (29%)	4 (100%)		7 (78%)	6 (100%)	

In the high Ki-67 group, the median overall survival of Ga-68 or In 111-positive patients was 10 (2.33-17.66) months, and that of negative patients was 9 (4.99-13.00) months (p=0.950) (Figure 1).

Discussion

In our study, although it was not statistically significant, the low Ki-67 scan-positive group had longer overall survival than the Ki-67 scan-negative group and in the high ki67 group, the median overall survival was longer in the scan-positive than it was in the negative group. Currently, there is no consensus on classification of grade 3 NETs. Some general characteristics and prognostic differences are present in grade 3 NET groups. We showed these differences in our study with the help of the Ki-67 index and Ga-68 PET CT/octreoscan.

Previous studies used 55% level as cut off Ki-67 value, but we analysed our data with the ROC curve method and we found our value to be 47%. Ki-67 cut off values should be interpreted with some cautiousness because Ki-67 values may vary in different centers. This may be occasioned by the the methodology, experience of the pathologist and heterogeneity of the tumor.

In our study, in both the low and high Ki-67 scan-positive groups, the pancreas was the most common primary site while the stomach was the most common primary site in the low Ki-67 scan-negative group. There was a discrepancy in primary sites in the literature. In poorly differentiated GEP-NETS with Ki-67 higher than 55%, the most common primary site was colon. In the well-differentiated group, the pancreas was the most common site [9]. It is worthy of note that the pancreas was the most common primary site in our study (54% of the whole patients). In contrast to our study, Fitzgerald et al. reported that high grade GEP-NETS were less likely to arise from the pancreas [16].

In our study, objective response rates to first-line chemotherapy were 13% for the low Ki-67 group and 47% for the high Ki-67 group. A recently published important report evaluating grade 3 GEPNECs has shown results similar to ours. In that study, GEPNECs with Ki-67 levels lower than 55% have lower response rates to platinum-based chemotherapy but GEPNECs with Ki-67 levels above 55% have higher response rates to platinum-based chemotherapy [9]. This report suggests that grade 3 tumors are not homogeneous and that there are two different tumor characteristics.

In another study, GEPNEC patients were divided into two groups according to Ki-67 levels under 55% and equal/upper 55%. Differentiation was added to the analysis, and it was discovered that patients with well-differentiated GEPNEC in lower Ki-67 groups had the best overall survival of 43.6 months, while the poorly differentiated group with a lower Ki-67 group had moderate overall survival with 24.5 months. The poorly differentiated group with a Ki-67 index $\geq$ 55% had 5.3 months ($p<0.0001$) [7]. In our study, we found patients with lower Ki-67 scan-positive group to be have the highest survival time-frame, just like this study. In the high Ki-67 scan-positive group, the median overall survival was longer than the scan-positive group. Millione et al used morphological differentiation with Ki-67 levels in their study [7]. There is no well-defined histological criteria for differentiation of neuroendocrine carcinomas and generally tumor grade. It is determined by a result of a single biopsy, so it is inadequate to obtain all the characteristics of tumors. Molecular imaging could help us obtain well or poorly differentiated tumors in whole body [17]. In well differentiated NETS, the target is the somatostatin receptors and the Ga-68 PET/octreotid scan targets these somatostatin receptors. So, they are useful for the identification of well differentiated NETs. Ga-68 PET CT is sensitive to well differentiated neuroendocrine tumors [18]. Although the Ga-68 PETCT scan is more sensitive, especially in small tumors or tumors bearing low density of somatostatin receptor expression than in octreoscan [19], both imaging tools are useful for detecting well differentiated neuroendocrine tumors. Therefore we used Ga-68 PET CT/octreoscan as a differentiation marker instead of morphological differentiation. Scan-positive patients were accepted as a well differentiated group, while, scan-negative negative patients were accepted as a poorly differentiated group.

The median overall survival period of the poorly differentiated lower Ki-67 group in Millione's study was longer than that of our low Ki-67 scan-negative group. Our low Ki-67 scan-negative group had the shortest overall survival in all our groups. The patients in the low Ki-67 scan-negative group had poor prognostic factors. For example 2 (50%) of these patients couldn't have any therapy, 75% had multiple metastatic regions and patient population was older than the others. These reasons could be responsible for the worse outcomes for this group.

In both high and low Ki-67 groups, scan-negative patients unexpectedly had lower response rates than scan-positive patients. In a study, 25% of the positive Ga-68 patients were in the poorly differentiated group [18]. It was previously demonstrated that NSE levels were associated with poor differentiation [20]. In our study, NSE levels were high in 58% of scan- positive low Ki-67 group patients, and in 50% of scan-positive high Ki-67 group patients. This data supports the hypothesis that the scan-positive group is not a unique clinical entity. It may include poorly differentiated tumor component with the well-differentiated group. It is possible that this chemotherapy response is associated with this poorly differentiated group.

Retrospective natures, limited number of patients are some limitations that our study faced. Also we didn't evaluate our patients morphologically due to lack of well-defined histological criteria for identifying well and poorly-differentiated grade 3 gastroenteropancreatic neuroendocrine tumors. We evaluated patients only with Ga-68/octreotid scan but not FDG PET CT scan. FDG PET CT is more sensitive in poorly differentiated and high grade tumors. PET CT could provide us with information about poorly differentiated components of a tumor [18].

Conclusion

In conclusion, we demonstrated differences and characteristics of grade 3 gastroenteropancreatic tumors. The median overall survival period was longer in patients with low Ki-67 group than high Ki-67 level group. In both the high and low Ki-67 groups, the patients in the scan-positive group had numerically longer overall survival compared to the scan-negative patients. The patients had excellent overall survival when they had both low Ki-67 and scan positivity in grade 3 gatroenteropancreatic tumor. The patients with diagnosed grade 3 gastroenteropancreatic tumor must be evaluated with all clinical, pathological, molecular and imaging methods to manage them successfully. These results need further evaluation with large prospective studies.

Conflict of interest

The authors declare that there is no conflict of interest.

Ethical approval

Erciyes University Clinical Research Ethics Committee (2020/72 29.01.2020).

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