The Gulf Journal of Oncology

Indexed By PubMed and Medline Database

Issue 40, September 2022
ISSN No. 2078-2101

The Official Journal of the Gulf Federation For Cancer Control

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Original Article

The Clinicopathologic Characteristics and Outcomes of Gastroentero–pancreatic Neuroendocrine Tumors – Experience from A Tertiary Cancer Center

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Abstract

Objective: Gastroentero–pancreatic neuroendocrine tumor (GEP NETs) are a heterogeneous group of tumors with variable behaviors. Our aim was to study the baseline characteristics and outcomes of GEP–NETs and to establish the impact of tumor grade and resectability on the survival.

Methods: A single center retrospective review of patients registered at SKMCH & RC Pakistan with the diagnosis of GEP–NETs was carried out from the Hospital Information System. The baseline characteristics of 134 diagnosed patients from January 2006 to August 2020 were analyzed. Overall survival (OS) and Disease Free Survival (DFS) was calculated using Kaplan–Meier curve. The impact of tumor grade and resectability was seen on the OS and DFS. Data was analyzed through SPSS version 23. Categorical parameters were computed using Chi–Square test, keeping p–value ≤0.05 significant.

Result: A large majority had Grade 1 disease **(59%)** along with localized stage at presentation **(73.1%)** as compared to Grade 2 **(23.9%)** and Grade 3 **(17.1%)** disease with metastatic stage at presentation **(26.9%)**. The 5 year OS according to tumor grade was, 88%, 57% and 0% in low, intermediate and high grade respectively. The 5–year OS was 94%, 79% and 43% in the completele, incomplete and in unresectable disease group, respectively.

Conclusion: GEP–NETs are rare tumors with good outcomes in Grade I and II and poor outcomes in grade III Neuroendocrine Carcinomas (NEC). Tumor grade and complete surgery of the primary tumor are important predictors of response outcomes and prognosis.

Keywords: Neuroendocrine Tumors, Outcomes, Resectability, Neuroendocrine Carcinoma

Introduction

Neuroendocrine tumors consist of a broad spectrum of malignancies that arise from neuroendocrine cells throughout the body. Neuroendocrine tumors are a heterogeneous group of epithelial neoplastic growths with variable behaviors and consequences. Although, there has been a worldwide increase in the prevalence of GEP–NETs, there have been fewer studies in Pakistan to fully comprehend this rare tumor. Therefore, it is important to know the clinical and pathological details of these tumors to better understand the different variations in respect to location, grading and behavior. Some clinical and pathological features of NETs are characteristic of the organ of origin, whereas the neuroendocrine tumors group as a whole, irrespective of anatomic site, shares other features[1].

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The literature available for GEP NETs has grown and developed during the past three decades. A rise in incidence of these tumors has been observed during the past few years probably either due to true incidence, increased awareness in healthcare professionals and/or public or early diagnosis due to readily available and advanced diagnostic techniques. GEP–NETs contribute to around 65–75% of all NETs arising in the body. Pancreatic NETs (pNETs) encompass roughly half of GEP–NETs and contribute to less than 3% of all primary pancreatic malignancies[2]. A large–scaled epidemiological survey of Gastroentero–pancreatic (GEP) NETs conducted on 2,845 patients in Japan estimated that the annual incidence of GEP–NETs was 1.01 per 100,000, which was lower than those in the US (2.85 per 100,000) and Norway (2.33 per 100,000). Such results suggest that racial differences may be present in the incidence of Neuroendocrine Tumors[3].

Neuroendocrine cells are extensively distributed throughout the body and neoplasms from these cells can arise at many sites. Majority of them arise in the gastrointestinal tract and collectively they are referred to as Gastroentero–pancreatic neuroendocrine tumors (GEP NETs). They include carcinoid tumors, pancreatic islet cell tumors (gastrinoma, insulinoma, glucagonoma, vasoactive intestinal peptidoma, and somatostatinoma), paragangliomas, pheochromocytomas and medullary thyroid carcinoma[4].

We aimed to determine the baseline characteristics and outcomes of GEP NETS, in terms of Overall Survival (OS) and Disease–Free Survival (DFS), along with an intention to establish the impact of tumor grade and resectability on the survival. To the best of our knowledge, such a study has not been conducted in the region of South–East Asia previously.

Materials and methods

This was a retrospective observational study, which included patients with Gastroentero–pancreatic Neuroendocrine Tumors (GEP–NETs) who were diagnosed from January 2006 to August 2020 at a tertiary care oncology hospital by the name of Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH & RC). The study population included patients selected through purposive sampling.

A total of 444 patients with neuroendocrine tumor were registered during the above–mentioned time–period, of which 134 patients were eligible for final analysis. We included all the histologically diagnosed primary GEP–NETs patients. Extra GEP NETs and the patients with dual histologies were not evaluated in this retrospective review. All the cases were identified by filtering out Gastroentero–pancreatic neuroendocrine tumors from the Hospital Information System (HIS). This study was approved by the Institutional Review Board of the SKMCH & RC, Pakistan.

GEP–NETs were histopathologically defined according to the WHO 2010 classification. Patients who had been diagnosed and treated before 2010 were re–defined. Patients were divided into three grades, comprising of Grade I, Grade 2 and Grade 3 according to the Ki–67 index. Grade 1 included patients with a Ki–67 index of less than or equal to 2%, Grade 2 included patients with values ranging from 3% to 20% while Grade 3 consisted of patients with a value greater than 20%.

According to different degrees of pathologic differentiation, all GEP–NETs were divided into two grades which were well–differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas. Well differentiated NETs were further sub–classified into low grade NET (GI) and intermediate grade NET (G2), whereas poorly differentiated NETs included high grade NET (G3).

The patient's age, gender, grade of tumor, stage of tumor at presentation, site of tumor, tumor type {either Sporadic or Multiple Endocrine Neoplasia (MEN)}, site of metastasis along with overall survival (OS) and disease free survival (DFS) were recorded. OS was defined as either the time interval since diagnosis until death or till the last follow–up, whereas DFS was defined as the time from diagnosis to progression in the stage of the disease.

Data was analyzed using the SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA). Kaplan–Meier analysis was used to estimate the cumulative OS rate while the log–rank test was used to analyze significances among the different groups; the two–tailed P values ≤0.05 were considered statistically significant.

Results

3.1 Clinicopathological Characteristics of GEP–NETs:

The mean age of the patients was 47 years, including 77(57.5%) male and 57(42.5%) female. It was found that a large majority had Grade 1 disease (59%) followed by Grade 2 (23.9%) and Grade 3 disease (17.1).

About 73.1% patients had localized disease at presentation, whereas 26.9% were metastatic. Only 3 patients were found to be associated with MEN I syndrome making it a total of 2.2%; all others were sporadic (97.8%). Most of the patients had symptoms related to localized disease (77.6%), 15.6% had symptoms related to NET, while remaining were metastatic (6.7%). Only 1 patient

was found to be asymptomatic, contributing a 0.7% of the total number of patients and was diagnosed incidentally.

Pancreas was found to be the most common site of primary tumor (45.5%), followed by small intestine and gastric. Liver was found to be the least common site of primary tumor (3.7%) but most common site of metastasis as described in the table 1. (Clinicopathological Characteristics of GEP–NETs)

Variable	Total	
	N = 134 N (%)	***P***
Sex		
Male Female	77 (57.5) 57 (42.5)	
Grade		
I II III	79 (59) 32 (23.9) 23 (17.2)	
Stage at Presentation		
Localized Metastatic	98 (73.1) 36 (26.9)	<.05
Symptoms at Presentation		
Localized Metastatic NET Symptoms Asymptomatic	104 (77.6) 9 (6.7) 20 (15.6) 1 (0.7)	
Type of Tumor		
Sporadic MEN–1	131 (97.8) 3 (2.2)	
Site of Primary Tumor		
Anorectal Appendix Esophagus Gall bladder Gastric Large intestine Liver Pancreatic Small intestine	7 (5.2) 5 (3.7) 2 (1.5) 4 (3.0) 24 (17.9) 5 (3.7) 1 (0.7) 61 (45.5) 25 (18.7)	

Table 1: Clinicopathological Characteristics of GEP–NETs

3.2 Overall survival

Based on surgery: the end point of interest was death or last follow up. Majority of patients had un–resectable disease at presentation 60 (44.77%), followed by the patients who had complete resection 41 (30.5%) and incomplete resection 33 (24.62%). A total of 31 patients died (23.1%), 2 in the complete resected arm (6.4%), 5 in partially resected (16.1%) and 24 in patients in un–resected arm (77.4%). As seen in **Table 2**, 95.1% patients were alive after surgery in the completely resected group, 84.8% in the incompletely resected group and 60% in the unresected group. The overall survival difference was significant (p value <0.05) for the resected–unresected group and incompletely resected–unresected group, whereas no significant difference in OS between complete resection and incomplete resection (**Figure 1**). The 5–year OS was 94%, 79% and 43% in the completele, incomplete and in unresectable disease group, respectively. Patients in the un–resected group were able to achieve a median overall survival of 23±3 months whereas, completely and incompletely resected groups were not able to achieve a median overall survival, as at the time of study submission, as approximately 70% of patients were still alive i.e. overall survival being 60 months.

Based on grading: the endpoint of interest in OS was death or last follow up. Most of the patients had low–grade disease 79 (58.9%), followed by intermediate grade 32 (23.88%) and high grade 23 (17.1%). A total of 31 patients died (23.1%), 17 (54.8%) in patients with high grade, 7 (22.5%) both with intermediate grade and low grade. Highest number of patients were alive with low grade tumor (91.1%) followed by intermediate grade patients (78.1 %.) Only 6 (26.1%) patients with high grade were alive (26.1%) **Table 3**. There was a significant difference in log rank –p value (<0.05) in patients with high grade versus low grade tumors, high versus intermediate grade tumors and low versus intermediate tumors (Figure 1). The 5–year OS was 88% in patients with low grade, 57% in patients with intermediate. High–

Type of Surgery	Total N	N of Deaths	Alive – N (%)
Complete Resection	41	2	39 (95.1)
Incomplete Resection	33	5	28 (84.8)
Un–Resected	60	24	36 (60.0)
Overall	134	31	103 (76.9)

Table 2: Overall Survival On The Basis Of Surgery

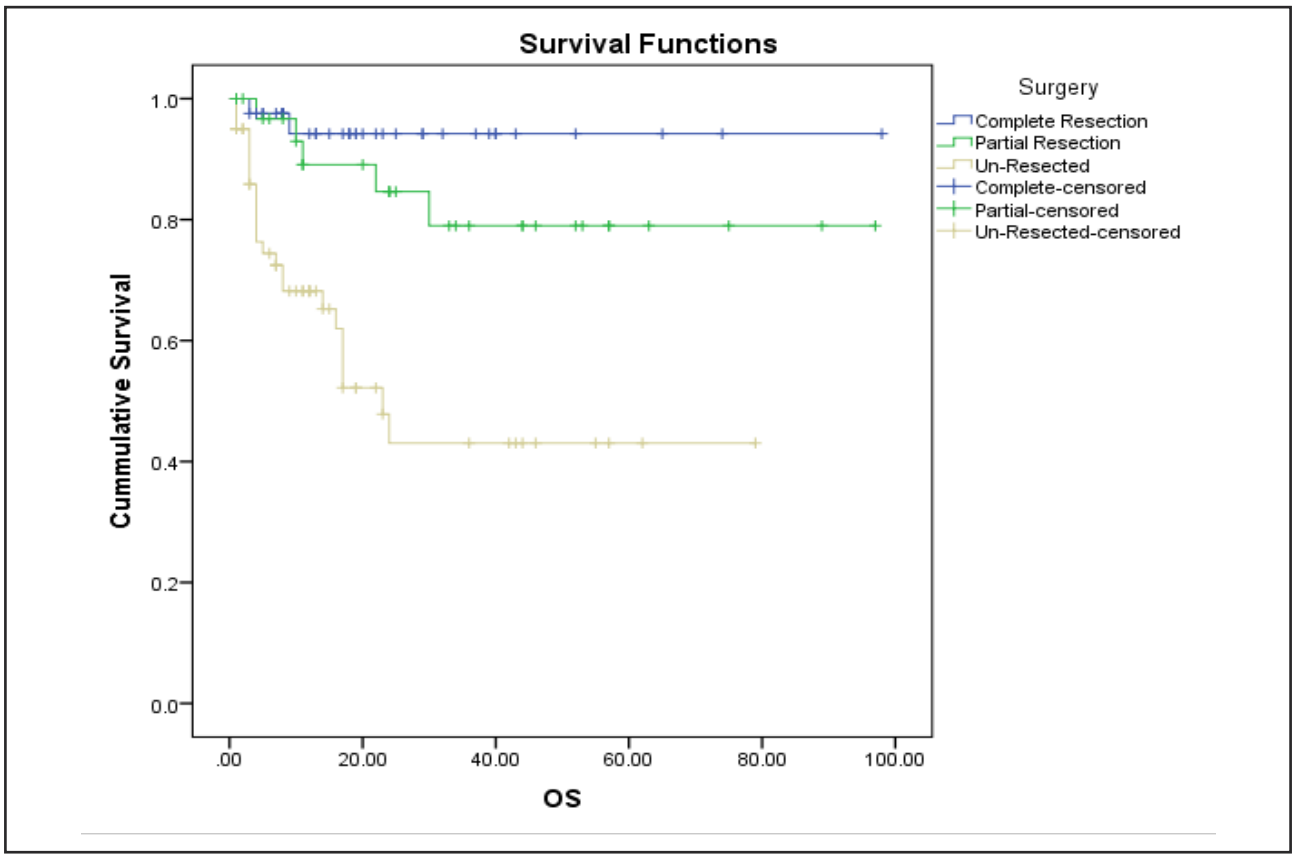

Figure 1: Kaplan–Meier Survival curves in patients with surgery according to Overall Survival

Grade	Total N	No of deaths	Alive – N (%)
High grade	23	17	6 (26.1)
Intermediate grade	32	7	25(78.1)
Low grade	79	7	72(91.1)
Overall	134	31	103(76.9)

Table 3: Overall Survival On The Basis Of Grades

grade tumor on the other hand were not able to survive the 5–year window and had a mdian survival of 8±4 months. Low and intermediate grade patients were not able to achieve a median overall survival, as at the time of study submission approximately 50% of patients were still alive i.e. overall survival being 60 months as shown in (**Figure 2)**

3.3 Disease free survival

Based on surgery: the endpoint of interest in DFS was disease progression or death after completion of therapy i.e. resection. A total of 14 (18.9%) patients had progression after resection; 5 (35.71%) in the completely resected group and 9 (64.29%) in the incompletely resected group, and the p value between these 2 groups was >0.05 **(Figure 3)**

The 5–year disease free survival was 60% in patients with incomplete resection and 74% in patients with complete resection of the primary tumor. Patients in both the groups did not reach their median disease–free survival, as at the time of study submission, more than 50% patient were still alive. **Table 4**

Based on grading: only 10 (14.49%) patients had progression after resection, 5 (50%) patients each in the intermediate and low–grade group **(Figure 4)**. The 5–year disease free survival was 76% in patients with low–grade tumors and 40% in patients with intermediate grade. Patients with intermediate grade tumor, however, were able to reach the median disease–free survival of 33 months only. **Table 5**

Disease free survival, on the basis of surgery, could not be seen in high–grade patients as surgery was not offered to them in lieu of metastatic disease

Discussion

Neuroendocrine tumors of the Gastroentero–Pancreatic (GEP) system are epithelial neoplasms with predominantly neuroendocrine differentiation and originate from diffuse

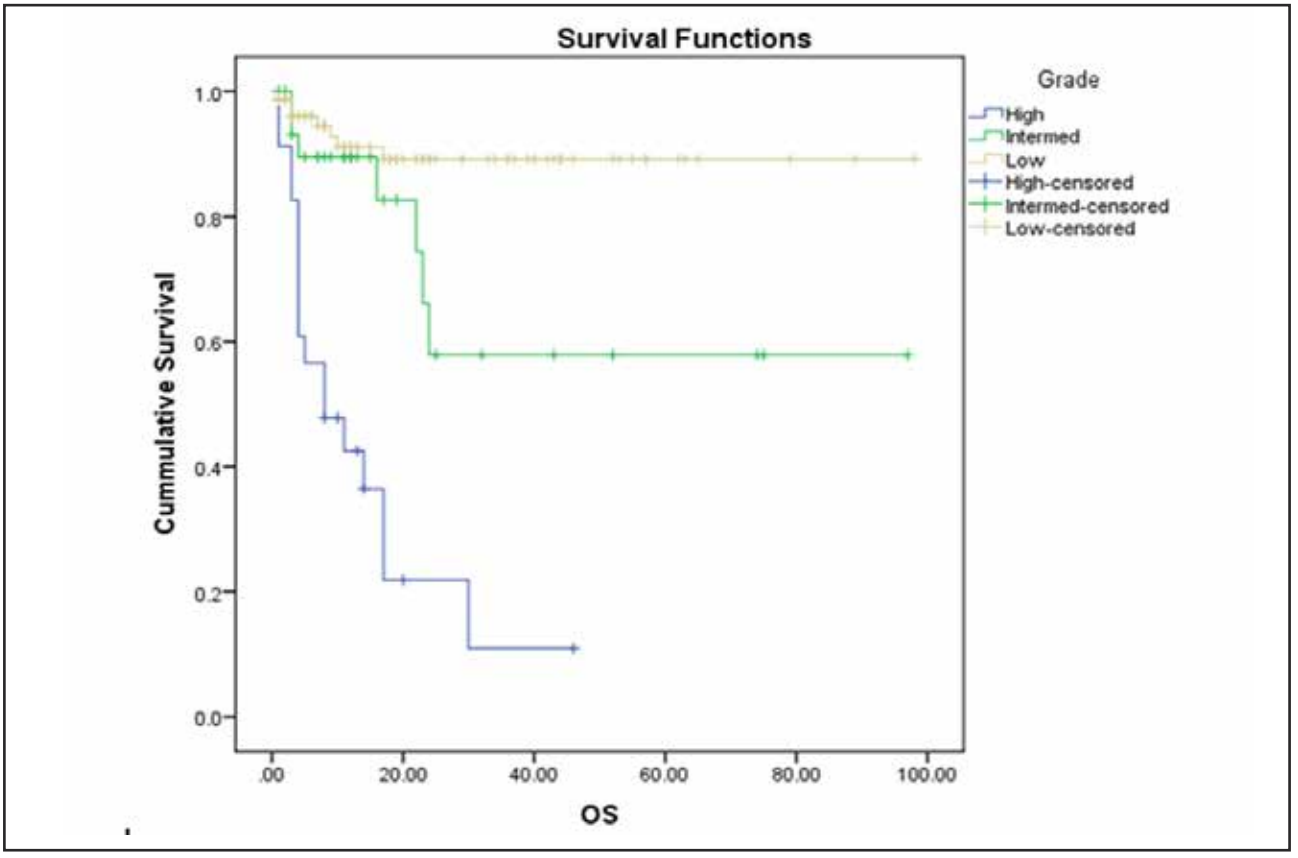

Figure 2: Kaplan–Meier Survival curves in patients on the basis of grading according to Overall Survival

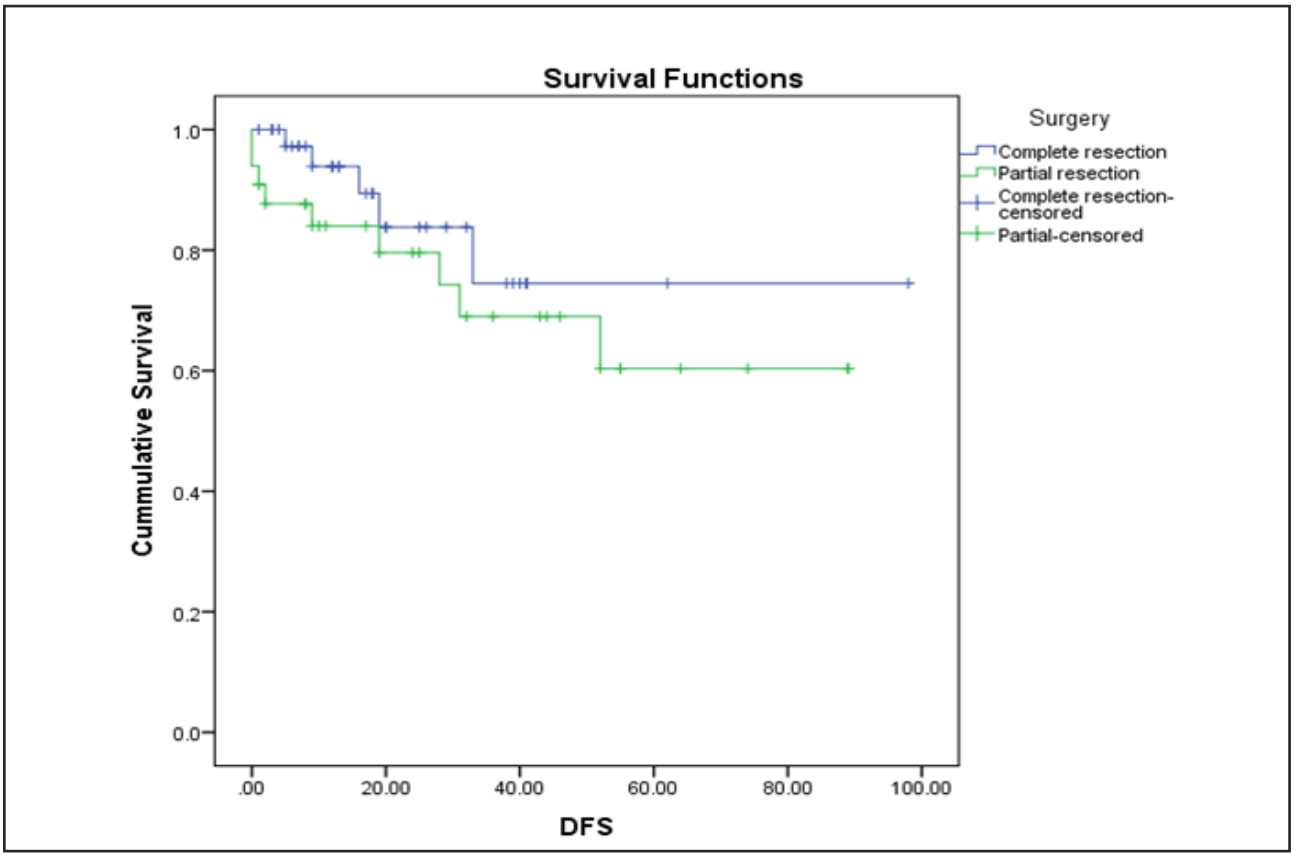

Figure 3: Kaplan–Meier Survival curves in patients with surgery according to Disease Free Survival

Surgery	Total N	N of Deaths	Alive – N (%)
Complete Resection	41	5	36 (87.8)
Incomplete Resection	33	9	24 (72.7)
Overall	74	14	60 (81.1)

Table 4: Disease Free Survival On The Basis Of Surgery

Grade	Total N	N of progressions	Alive – N (%)
Intermediate grade	15	5	10 (66.7)
Low grade	54	5	49 (90.7)
Overall	69	10	59 (85.5)

Table 5: Disease Free Survival On The Basis Of Grades

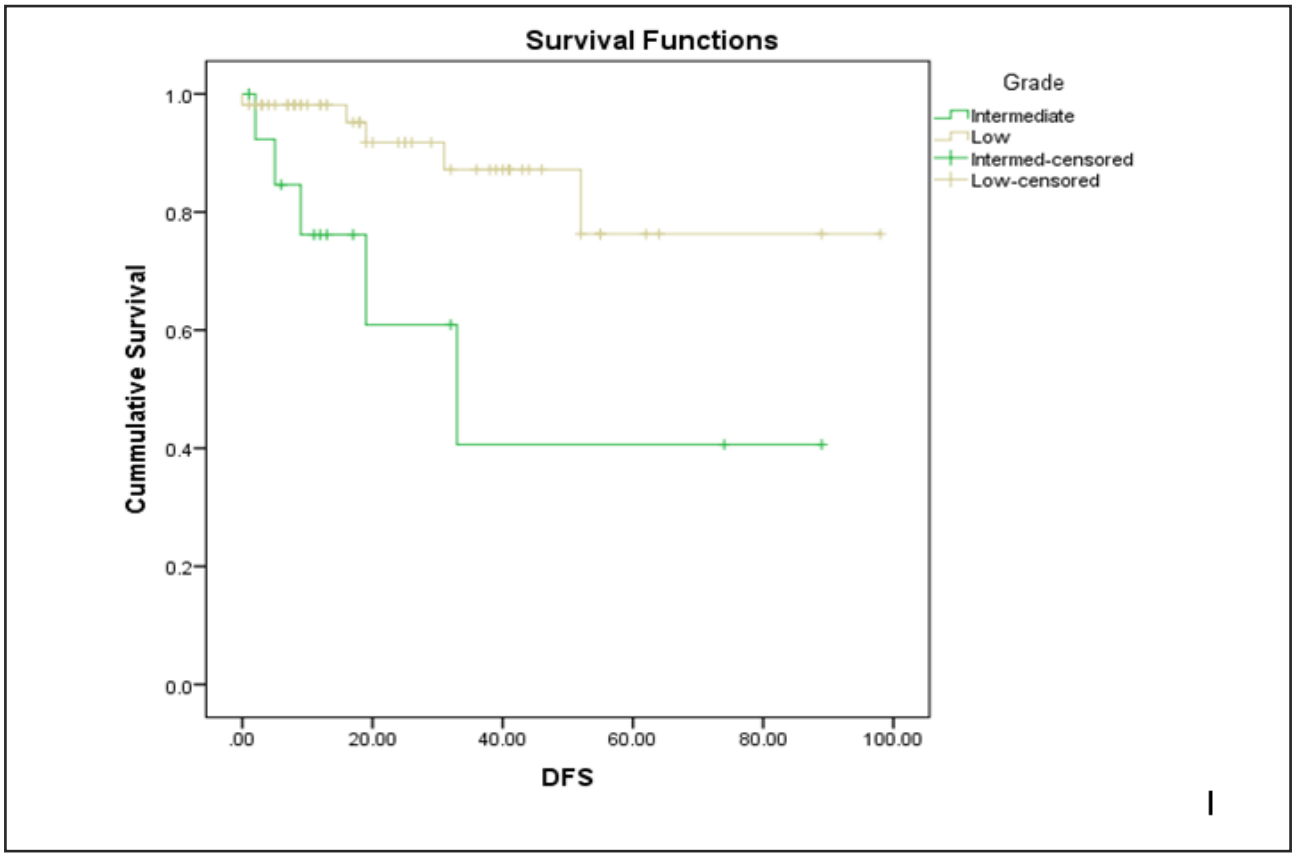

Figure 4: Kaplan–Meier Survival curves in patients on the basis of grading according to Disease Free Survival

endocrine system located in the gastrointestinal tract and the pancreas. They represent 2% of all GI tumors. It has been seen that incidence of NETs is steadily increasing[6]. Neuroendocrine carcinomas can occur in the digestive tract, lungs, pancreas, thyroid, adrenal glands and other organs, but they are most common in the digestive tract[7].

In this study, the clinico–pathological features of GEP–NETs were retrospectively analyzed along prognosis in terms of overall survival (OS) and disease free survival (DFS). Majority of the patients were male (57.5%) compared to females (42.5%), with a male to female ratio of 1.3:1 and a mean age of 47years. This is similar to other studies where the male are affected slightly more frequently then female (I.5:1) [3,8]. There were 59% patients who were low grade (G1), 23.9% were intermediate grade (G2) and 17.2% were high grade (G3). Fang C, et al (2017 Jun 21) also showed comparable percentages, where 51.4% were GI, 22.8% were G2 and about 25.8% were G3[8], as well as the Netherlands whose results were likewise (Korse CM, et al, 2013) [9].

NENs can be categorized into functional and non–functional tumors according to the presence or absence of symptoms associated with hormone production (Klimstra et al., 2010) [10]. Krystallenia et al found that approximately 10% are associated with Multiple Endocrine Neoplasia (MEN)–1 syndrome but GEP–NENs can also be found in Neurofibromatosis type 1 (NFl), Von–Hippel–Lindau (VHL) disease, tuberous sclerosis and occasionally in familial

adenomatous polyposis (FAP)[5]. The results of this study, however; had only 3 patients (2.2%) had endocrinal symptoms of MEN–1 syndrome whereas the remaining patients had sporadic symptoms due to localized disease. This low number of associated syndromes in current study can be attributed to its geographical variations.

Though, these tumors are extensively distributed throughout the different organs in the body. In this study, the most common primary site was the pancreas (45.5%). The small intestine (18.97%) in the GI tract followed this while the least involved sites were the esophagus (1.5%) and liver (0.7%). A similar study conducted in China also showed the pancreas as the major site (53.3%) whereas the rectum was the most recurrent site within the GI tract, while the colon was the least involved location[11]. In contrast, pancreatic NENs were only the third most common site for NENs (Yao et al., 2008) [12].

At the time of presentation, we found that 73.1% of patients had a localized disease, while 26.9% had metastasis. The liver was the most common site of metastasis (19.2%). In the study by Yongchao Zhang et al, there were 14 cases among the 49 patients with distant metastases (28.6%) to which our results closely match[13]. However, Yu–Jie Zeng, et al showed slightly lower cases of distant metastasis at diagnosis, with an occurrence of 19.7% (24/122). Their results also showed the liver as the most frequently involved organ, where metastasis had occurred among 29 (90.7%) of 32 patients during the course of the disease.) [11].

In the current study, a total of 74 (55.2%) patients underwent surgery while the remaining 60 (44.7%) did not have any type of surgery for the primary tumor. Among the patients that underwent surgery, complete resection was done in 41 (55.4%) patients and palliative surgery in 33 (44.6%) patients. In addition, about 65 (48.5%) patients received systemic anti–cancer therapy, 8 (5.9%) received Somatostatin analogues and 61 (45.5%) did not receive any systemic therapy. On the other hand, the study conducted by Yu–Jie Zeng, et al had a large percentage of patients that underwent surgery (90.2%, 110/122) where the purpose was curative intent in 78.2% (86/110) of the cases and palliative care in 21.8% (24/110) of the patients[11].

A study of 360 patients with midgut NETs and liver metastases in the United Kingdom and Ireland reported 209 (58%) had resection of their primary tumor, 12 (3%) had surgical bypass and 17 (5%) were explored and found to be unresectable. The median survival of those who had their primary tumor resected was significantly longer (9.9 years) than in those who did not undergo operation (4.7 years), or for those undergoing bypass (5.6 years), or those who were explored but not resected (6.7 years) [14]. In a recent study from Milan, resection of primary tumors was carried out in 67% of patients, and the median survival of this group was 138 months in contrast to 37 months who did not have, their primary tumor resected. This survival benefit of resecting the primary also held up in the 103 patients who did not have their liver metastases resected[15]. In this study, however, patients in the un–resected group were able to achieve a median overall survival of 23±3 months while complete and incompletely resected groups were not able to achieve a median overall survival due to approximately 70% of patients being alive at the time of submission, i.e. overall survival being 60 months.

The limitations of this study was that the role of systemic and/or target therapy was not evaluated on the overall survival and disease free survival.

Conclusion

GEP NETs are rare tumors with good outcomes in grade I and II and poor outcomes in grade III Neuroendocrine Carcinomas (NEC). Overall Survival and Disease Free Survival have proved to be comparatively higher in the presence of resectable and low grade disease. Therefore, the grade of the tumor and complete surgery of the primary tumor are important predictors of response and prognosis.

Statement conflict of Interest: No conflict of interest to disclose.

Acknowledgements: Abdul Karim; Quality Assurance Officer, Shaukat Khanum Memorial Cancer Hospital and Research Centre Peshawar Pakistan.

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