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Original Article

Well differentiated neuroendocrine tumors, a single center experience

Ece Esin*, Berna Oksuzoglu, Erkan Erdur, Guliz Ozgun, Umut Demirci

University of Health Sciences, Dr. A.Y Ankara Oncology Education and Research Hospital, Department of Medical Oncology, Demetevler, Ankara, Turkey

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ABSTRACT

Purpose: The aim of this study is to analyze the demographic, histopathologic features of Neuroendocrine tumor (NET) cases and to underline the treatment approaches over seven years period in a high-volume cancer center.

Methods: This study designed as a retrospective evaluation of NET registry data from a single medical oncology clinic between January 2012 and November 2017.

Results: A total of 72 patients'? data were registered. The median age was 54 (18–84) years. The three most common sites of diagnosis were pancreas (19 cases, 26.4%), unknown primary with liver metastasis (15 cases-20.8%) and lung (10–13.9%). There was no association between the extent of disease and grade of NET ($p = 0.73$). Apart from pancreatic NETs, there was no difference in the stages of disease presentation ($p > 0.05$). Globally, estimated 5-year overall survival (OS) rate was 77.5% and 10-year OS rate was 57.8%. There was no statistically significant difference in estimated 5- year OS rates of comparison between grade 1 and grade 2 NET's (69.9 vs. 91.8%, $p = 0.19$). In addition, Ki67 proliferative index did not make any difference in estimated 5- year OS rates (78.1 vs 77.7%, $p = 0.71$).

Conclusions: The multimodality treatment, site specific approaches and radionuclide therapies lead to better response rates and a longer survival in patients. Although there is a difference in distribution and presentation of NET cases compared to previous publications, optimal treatment yields a good Results?. Wherever possible, treatment of NETs is optimally scheduled by a multidisciplinary team, data collection should be centralized and audited by the team to make a clear conclusion for a less acknowledged tumor type.

1. Introduction

Neuroendocrine tumors (NET's) are relatively rare tumors, the annual incidence in the United states in 6.98/100000 population which is reported to be increasing.[1,2] The annual prevalence of gastroenteropancreatic NETs (GEP-NET) as a second common malignancy of digestive system, is more than the sum of prevalence of gastric and pancreatic carcinomas.[3,4]

NETs are epithelial neoplasms which can originate from any neuroendocrine cell throughout the body, therefore some of clinical and pathological features are shared while others are particular for the site of origin.

Various classifications were suggested to group these tumors; lastly World Health Organization (WHO) have published 2010 NET classification which includes the consensus report. According to WHO, Gastroenteropancreatic (GEP) NET are classified as NET grade 1 (G1), NET grade 2 (G2) and neuroendocrine carcinoma (NEC) grade 3 (G3). The grading and proliferation index has prognostic importance. Additionally; site of origin, stage of disease and site of metastasis have prognostic impact on survival of patients.

During the last few years, there have been important advances in the diagnosis and management of NET as several treatment options have been made available even for patients with advanced disease, including targeted agents, radionuclide therapies.

The aim of this study is to analyze the demographic, histopathologic features of NET cases over seven years period in a high-volume cancer center.

2. Methods

This study designed as a retrospective evaluation of NET registry data from a single medical oncology clinic. Between January 2012 and November 2017, all of the patients who were carrying tumors in neuroendocrine histology with well differentiated

* Corresponding author.
E-mail address: dr.eceesin@gmail.com (E. Esin).
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characteristics (low-intermediate grade, less than 20 mitoses per high power field and less than 20% Ki-67 index) were retrieved from data registry system. The search of following questions were made 1) general administrative information 2) demographic characteristics 3) clinical and histopathological features (primary tumor sites, the number and site of metastasis, proliferative indexes of tumors, clinical symptoms if associated any) 4) immunohistochemical results of biomarker tests, including synaptophysin, chromogranin A 5) results of imaging tests (computed tomography, magnetic resonance imaging, ultrasonography) 6) results of nuclear imaging techniques 7) use of currently available local treatment options to primary tumor site (surgery, cytotoxic chemotherapy, radiation) and liver directed treatment to metastasis (Radiofrequency ablation, chemoembolization) 8) Any molecularly targeted therapy or theranostic treatment options.

The staging system was not unified during the data entering period therefore regarding the extend of disease, tumors are standardized as localized (primarily resected or resectable) regional or distantly metastatic. Tumor grading was done according to WHO criteria; if both of Ki67 and mitotic count was present, the higher one is selected to classify the tumor. WHO 2010 criteria were accepted to classify these tumors (NET grade 1: mitotic count <2/10 high power field, Ki67 < 3% and NET grade 2: mitotic count 2-20/10 high power field, Ki67 3–20%).[2]

Comparative statistics between independent groups were performed using the Chi-square test for categorical variables and using the Mann–Whitney test for continuous variables. The confidence interval was accepted as 95% throughout the analyses. Survival outcomes were assessed using the Kaplan Meier approach, and subgroup analyses were performed using the log-rank test. All statistical analyses were performed using IBM SPSS software version 21 (IBM Inc., Armonk-NY, USA).

3. Results

3.1. Patient characteristics

In seven years period, a total of 72 patient's data were registered to a database. Regardless of anatomical site of origin, all patients who fulfills the pre-defined histological criteria were included. The consort diagram is shown in Fig. 1.

The median age of low and intermediate grade NET patients was 54 in a range of 18–84. The peak age group at diagnosis was 45–60 years. There were no gender differences as women/men ratio was 0.9/1 (35/37). Patient characteristics were outlined in Table 1. The three most common primary diagnosis were pancreas (19 cases, 26.4%), unknown primary with liver metastasis (15 cases-20.8%) and lung (10–13.9%) low grade NETs.

In 12.5% (9 cases), there were carcinoid symptoms at the time of diagnosis and 80.6% of cases has any other symptom. Abdominal pain was the leading symptom (24 cases-33.3%), which is followed by dyspepsia and abdominal distension (12 cases-20%). In 37 of cases, there was any metastasis in at least one of the organs; the most common metastatic presentation belongs to ileal NETs (13.5%) after the pancreatic cases (37.8%). According to WHO 2010 classification, 37 cases (53.6%) were presented with grade 1 NET and 32 patients (46.4%) were presented with grade 2 NETs. Ki67 percentage was reported as $\leq$2% in 56.9% of cases whereas 3–20% in 43.1% of cases. WHO classification and the pathologic criteria of GEP-NET cases according to embryologic site of origin were outlined in Table 2. There was no association between the extent of disease and histological grade of NET ($p = 0.73$). However, more patients were diagnosed with metastasis in intermediate grade according to Ki67 index ($p < 0.05$). Apart from pancreatic NETs, there was no difference in the stages of disease presentation ($p > 0.05$). However, pancreatic NET cases were diagnosed significantly more in an extensive stage ($p = 0.03$).

3.2. Treatment methods

Overall, 44 patients (61.1%) underwent primary curative surgery. No palliative surgery (metastasectomy) was done. In gastric and appendicular NETs, 6 over 7 cases were treated primarily by surgery whereas 36.8% of pancreatic NET patients were unable to get operated at diagnosis.

Somatostatin receptor imaging was done in 46 patients and in 29 of imagings (63%) somatostatin uptake was observed. In 6 patients (8.3%), radionuclide therapy was utilized. Somatostatin receptor antagonists (SSRA) were used as a first line treatment in 28.6%, as second line in 15.7% and as a third line treatment in 4.3% of cases. SSRA's were not recommended for 11.7% of metastatic patients. Octreotide was the choice of treatment in 58.8% of patients and lanreotide was used in 41.2%. In 8 patients (10.8%), chemotherapy was needed to alleviate disease symptoms in patients with intermediate mitotic indexed NETs. In liver metastatic cases, liver directed local ablative techniques were utilized in 6.4% (4 cases). Treatment details were summarized in Table 3. Targeted therapies were rarely used. Sunitinib was the choice in second line treatment in six patients and in one metastatic pancreatic NET case everolimus was started in 3rd line treatment after progression with sunitinib.

In the data registry, for metastatic patients, median 35.7 months follow-up time was recorded (1–198 months). Median time to first progression was calculated as 45 months (3.8–164.9). Twelve patients were recorded as exitus and cancer specific mortality was recorded in only four cases. Globally, estimated 5-year overall survival (OS) rate was 77.5% and 10-year OS rate was 57.8%. There was no statistically significant difference in estimated 5- year OS rates of comparison between grade 1 and grade 2 NET's (69.9% vs. % 61.2, $p = 0.36$) (Fig. 2). In addition, Ki67 proliferative index did not make any statistically difference in estimated OS rates (%78.1 vs % 77.7, $p = 0.66$) (Fig. 3).

4. Discussion

In this study, it is aimed to investigate the diagnostic approaches and treatment modalities of NET cases seen in our medical oncology center and make a self-criticism to provide maximal benefit for the patients.

A total of 72 low-intermediate grade NET cases were seen in our cancer clinic, during the six-year medical oncology clinic NET registry. According to our results, pancreas is the most common site of origin. In the second place, patients were diagnosed with liver metastatic primary unknown NETs and the third common diagnosis was the bronchogenic NET's. There has not been any significant change in the distribution of most commonly seen NET's over time. According to NCI's SEER (National Cancer Institute Surveillance, Epidemiology, and End Results Program) data, small intestine (1.05/100000) is the leading site of origin of GEPNETs which is followed by rectum (1.04/100000). The distribution of NET origins depends on etiology, geographic area in which the oncology center locates and the area of expertise of consultant physicians. Therefore, the most common diagnosis differs in our center compared to previously published large series of NET's.[3,5]

The mean age of diagnosis in our database was 54 and the peak diagnostic age was 45–60 years. This age distribution is in parallel with Asian population.[6,7] In western countries NET's were diagnosed 10 years later for all primary sites.[3,8,9] There were no gender differences in our NET cases in general and also in relation with primary sites. However, in Chinese and Taiwanese population male

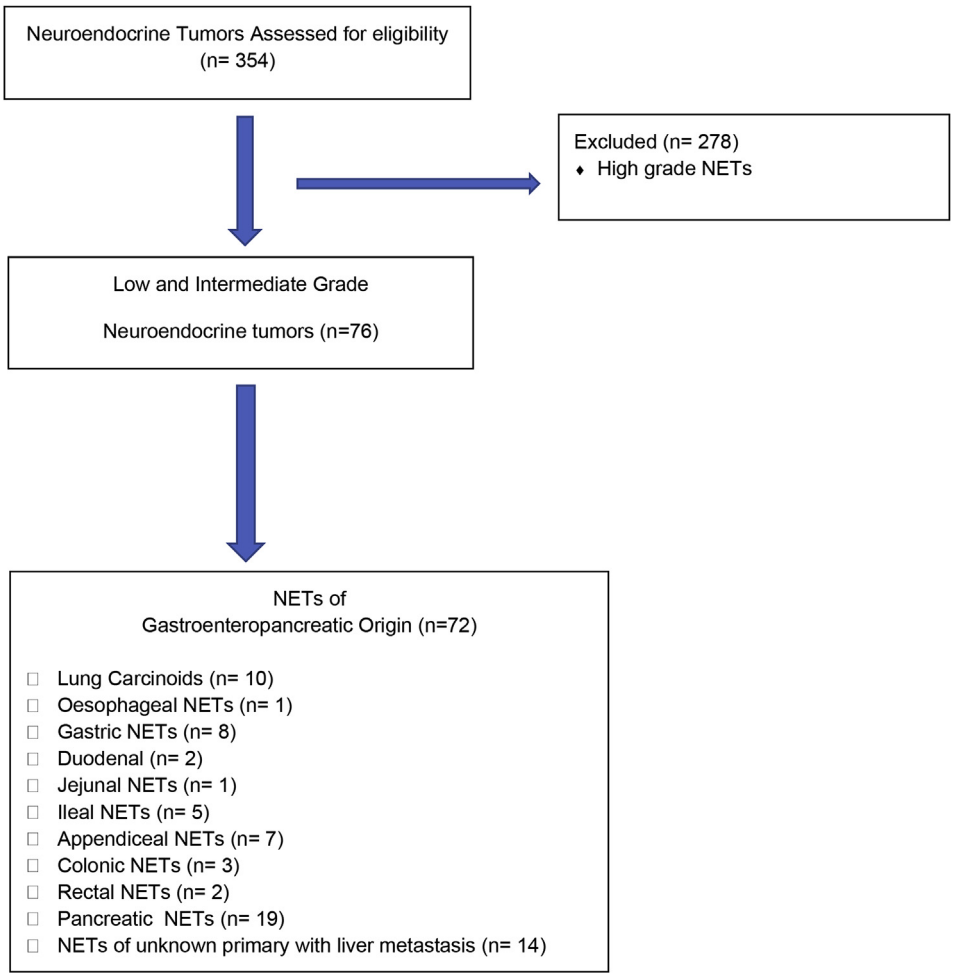

Fig. 1. Consort Diagram. NET: Neuroendocrine tumor.

Table 1
Patient characteristics (n = 72).

Characteristic	
Age, mean (range), year	54 (18–84)
	No. (%)*
Male sex	37 (51.3)
Proliferation index	
Ki67 ≤ 2%	41 (56.9)
Ki67 3–20%	31 (43.1)
Grading	
Grade 1	37 (51.4)
Grade 2	32 (44.4)
Missing/unknown	3 (4.2)
Stage at diagnosis	
Localized	27 (37.5)
Regional	7 (9.7)
Metastatic	37 (51.4)
Missing/unknown	1 (1.4)
Carcinoid syndrome at presentation	9 (12.5)
Any Symptom at Presentation	58 (80.6)
Anatomic distribution	
Foregut	21 (29.2)
Midgut	11 (15.3)
Hindgut	6 (8.3)
Pancreatic	19 (26.4)
Unknown primary with liver metastasis	15 (20.8)

Table 2
WHO classification and the pathologic criteria of NET cases according to site of origin.

		Grade (n = 67)		Ki-67 Index (n = 72)	
		1	2	≤2%	3–20%
		N-%	N-%	N-%	N-%
Involved site	Foregut	10–27.1	9–28.1	8–30.8	4–11.4
	Midgut	5–13.5	6–18.7	9–34.6	2–5.7
	Hindgut	4–10.8	2–6.3	2–7.7	4–11.4
	Pankreas	9–24.3	10–31.3	5–19.2	13–37.1
	Primary unknown with liver metastasis	9–24.3	5–15.6	2–7.7	12–34.3

Table 3
Treatment features (n = 72).

	n-%	
Surgery	44–61.1	
Liver Directed Therapy		
Chemoembolization	2–2.8	
Y-90 Microsphere Treatment	2–2.8	
None	68–94.4	
		Median PFS (median, %95 CI)
Chemotherapy Choices		
Fluorouracil-Streptozocin	3–4.2	4.1 (2.7–6.3)
Capecitabine-temozolomide	2–2.8	2.5 (1.9–4)
Temozolomide monotherapy	3–4.2	5.3 (2.5–7.9)
Somatostatin Receptor Antagonists		
Octreotide	20–58.9	
Lanreotide	14–41.1	
None	37–51.3	
		Median PFS (m, range)
Targeted therapies		
Sunitinib	6–8.3	9.3 (0.9–14.8)
Everolimus	1–1.4	3.4

Y-90: Yttrium-90 radioisotope.
PFS: Progression free survival.
m: months.
CI: Confidence Interval.

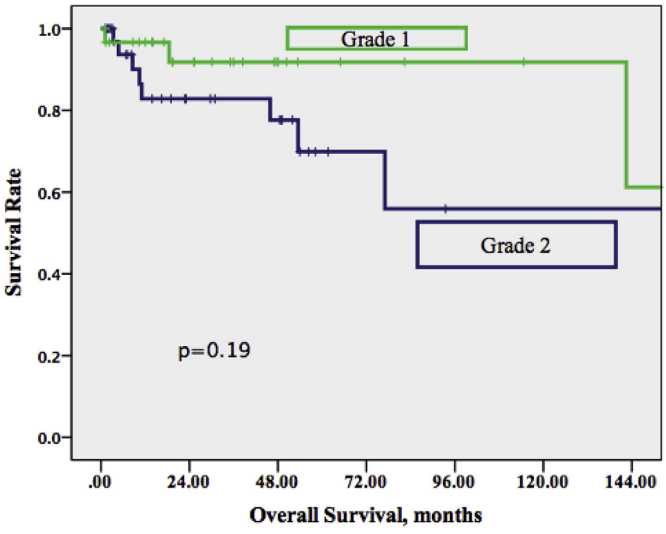

Fig. 2. Overall survival rates according to grade.

patient comprised gastric and rectal NET's and female patients occupy the majority in pancreatic NET's. In western population, gastric NET's did not differ in males and females however rectal and pancreatic NET's dominated in males.[8,10]

A prominent characteristic of GEP-NET's is the production of biologic amines (serotonin, 5-hidroxyindolaceticacid) which are

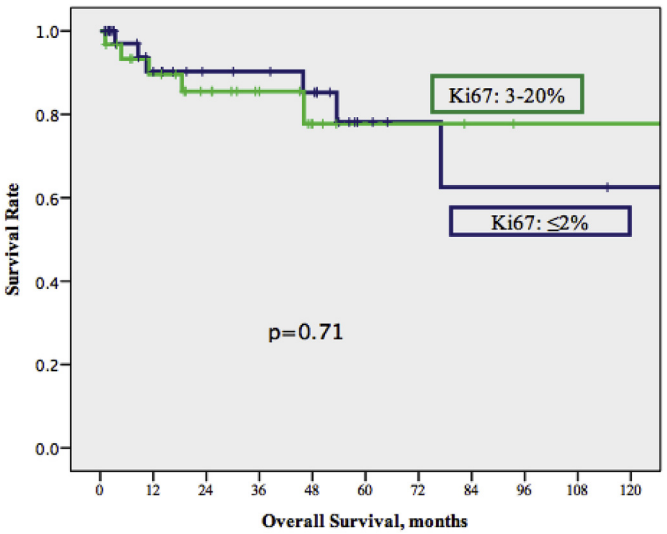

Fig. 3. Overall survival rates according to Ki67 level.

dependent on the site of embryological origin of the tumor. In the presence of liver metastasis or when the primary site of origin is lungs or ovary in which the amines bypass liver degradation, serotonin and its products leads to development of carcinoid symptom. Patients may develop flushing, diarrhea and abdominal pain and rarely bronchospasm. This complex of symptoms occurs infrequently in NET's, less than 10%.[11,12] In our population, the rate of carcinoid symptoms was 12.5%. Three NET's from lung, four pancreatic NET cases and 2 primary unknown liver metastatic case was presented with carcinoid symptoms. In previous reports, NET's diagnosis is incidental in 40–60% of cases. Whereas, in our registry 78.4% of patients have any kind of symptom, incidental NET finding rate is 18.9%. The frequency of carcinoid symptom and the rate of symptomatic patients were more than reported before but in parallel with results of published data of our geographical area.[13] Our clinic is a tertiary reference center, which accepts consultations across the country however this report only consist of single medical oncology center data hence may be biased.

Therapy of neuroendocrine tumors have changed dramatically in recent decade. In general, treatment is based on the intrinsic features of tumors such as site of origin, extent of disease, proliferation rate (Ki-67 and grade). A number of classical options are still important such as surgery for local disease, chemotherapy; and there are some advances such as long acting somatostatin analogs, molecular targeted agents and theraneustic modalities (peptide receptor radionuclide therapy-PRRT).

In this cohort, 37.5% of NET cases were diagnosed with localized disease, 9.7% as regional and 51.4% as metastatic disease. On the other hand, surgery would have been an option as definitive treatment in 61.1% of cases. Cytotoxic chemotherapeutics have been

the treatment modality of choice before the availability of modern knowledge in NETs. It is well known from older, retrospective analysis that alkylating agents and fluorouracil have some efficacy in well-differentiated NETs. On the other hand, especially cumulative toxicity of dacarbazine and streptozocin in such long-standing tumors lead clinicians to seek other options. A phase II study of temozolomide and thalidomide was reached 45% response rate (RR) and capecitabine and temozolomide combination yielded 70% RR with 18 months of progression free survival (PFS).[19,20] Currently, chemotherapy is used in patients with high tumor burden and when there is a need for rapid response especially in symptomatic and rapidly progressive disease.

Among our cohort, 37 patients (51.4%) were diagnosed as grade 1 and 32 patients (44.4%) diagnosed as grade 2. There was no statistically difference in distribution of grades according to embryological NET origin. Thirty-two (44.4%) of patients were having Ki-67 index of 3–20 and in 20 of them (60%) chemotherapy was needed to control the disease burden. Only one of grade 1 patients needed temozolomide monotherapy during the follow-up. Median PFS was recorded with Streptozocin-Fluorouracil as 4.1 months and with Capecitabin-Temozolomide as 2.5 months. These results are lower than reported before, might be related to the choice of patients and low number of sample size.

The embryological origin of neuroendocrine tumors creates a cell surface receptor characteristic, which are somatostatin receptors (SSTR) 1-5 that can be used for diagnostic, prognostic and therapeutic purposes. There are two ways of targeting SSTR as a treatment modality. One is long acting SSRA to alleviate the carcinoid symptoms and preventing long term sequela (nutritional deficiencies, congestive heart failure, mesenteric fibrotic changes) besides having an antiproliferative efficacy. Retrospective studies have previously shown that long acting SSRA's have cytostatic effect with 5–10% response rate (RR).[14–16] Two placebo-controlled trials (PROMID and CLARINET) have showed that long acting SSRA's may have an antiproliferative effect. A prolongation of time to progression in midgut low grade NET's was shown with long acting octreotide (14.3 vs. 6 months).[17] In the CLARINET study population which includes a variety of GEP NET cases, long acting lanreotide increased to progression free survival from 18months to 32.8 months.[18] In our group of patients, Octreotide was applied to 20 cases (27.8%) and Lanreotide to 14 cases (19.4%). There was no statistical difference in progression free survival rates between two types of SSRA's ($p = 0.88$).

A well-established treatment modality for well-differentiated NET's is therapy with β emitting radiolabeled peptides (theraneustic approach). The response rate is directly related to density of SSTR on tumor cell surface. [21,23] A study of ^{177}Lu-DOTATATE showed a at least partial response in 30% of 310 patients, additionally median TTP was 40 months.[21] In a phase III, multicentric study, NETTER-1, ^{177}Lu-DOTATATE was compared to high dose octreotide (60 mg/month). The result of this study showed that the risk of progressive disease or death was 79% lower in ^{177}Lu-DOTATATE group as well as RR was significantly higher (18% vs. 3%) in Lu-arm.[22] In our clinic, theraneustic modalities became available after December 2016. In total, 6 patients were treated since 2016 with radionuclide therapy: Four of the patients as a third line treatment approach, two of them as a second line. Response rate in our cases who were treated with radiolabeled peptides was 33% and median PFS was calculated as 26months. Considering that ^{177}Lu-DOTATATE was used in later stages of disease, RR and PFS results were in parallel with previous reports. Low number of cases is related to time interval of patient selection. As a result, patients should be considered earlier for radiolabeled particles in the therapy course.

Several pathways of intracellular signal transduction have been discovered in NET's, a number of targeted therapies have been tested in phase III trials. Components of mTOR pathway is one of the targets which is found to be activated. An oral inhibitor of mTOR, everolimus, was tested against octreotide in two phase II trials showing efficacy. Later on, RADIANT-3 prospective phase III study tested 10 mg everolimus against best supportive care in 203 pre-treated pancreatic NET patients with documented disease progression in past twelve months.[24,25] Progression free survival advantage was shown (11months vs. 5.6months, HR:0.35). In a similar way, RADIANT-4 trial was a study in NET's also demonstrating a PFS benefit of 7 months also including lung carcinoids.[26] Another potential target for NET's is angiogenesis. It was shown that vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are expressed higher in NET's.[27,28] Sunitinib is a multi-potent tyrosine kinase inhibitor which exhibits antiproliferative and antiangiogenic activity. In a multicenter phase III in pNET patients a PFS of 11.4 months over 5.5months with placebo was recorded (HR 0.42, 95%-CI 0.26–0.66, $p < 0.001$).[29] In this patient cohort, sunitinib was chosen as a second line option in six patients in which median OS was not reached, although progression was detected in all of them. This may be explained by the efficacy of multimodality, sequential therapeutic approach to NETs. One case has started everolimus in third line who is still on 5th month of therapy without any progression.

Major limitation of this study is relatively low number of sample size. This might have created a bias in power analysis. Survival differences in subgroups of patients according to proliferative indices and therapy modalities may have influenced by low number of sample size and unequal distribution of risk factors between subgroups.

5. Conclusion

This specific patient cohort registry demonstrated that well-intermediate differentiated neuroendocrine tumors are diverse in nature but also share some common characteristics. The multimodality treatment, site specific (liver directed etc.) approaches radionuclide therapies lead to better response rates and a longer survival in patients. Although there is a difference in distribution and presentation of NET cases compared to previous publications, optimal treatment yields a good response. Wherever possible, selection of treatment in NETs is optimally scheduled by a multidisciplinary team, data collection should be centralized and audited by the team to make a clear conclusion for a less acknowledged tumor type.

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