Distinct Prognostic Factors in Sporadic and Multiple Endocrine Neoplasia Type 1-Related Pancreatic Neuroendocrine Tumors

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ABSTRACT

Pancreatic neuroendocrine tumors (PNET) may develop sporadically or in the context of hereditary syndromes. In patients with multiple endocrine neoplasia type 1 (MEN1), PNET is the leading cause of death. Our aim was to compare the mortality risk in sporadic and MEN1-related PNETs and identify high-risk populations. A retrospective Surveillance, Epidemiology, and End Results database analysis of patients with PNET was used. Patients with MEN1 were defined by syn/metachronous pituitary adenoma. Clinical data were retrieved, and all-cause mortality (ACM) risk was compared in univariate and multivariable analyses. The cohort included 569 patients (46.6% males) with sporadic (n = 542) and MEN1-related (n = 27) PNETs. Age at diagnosis of MEN1-related PNET was significantly younger than with sporadic PNETs (mean age 49.2 ± 16.7 vs. 61.6 ± 12.7 years, respectively; p < 0.001). Survival analysis showed a trend for a better outcome in patients with MEN1-related vs. sporadic PNET (Log-rank, p = 0.09) and in subgroup analysis for patients with advanced disease (p = 0.08). Furthermore, among patients followed expectantly, those with MEN1-related PNET had lower ACM risk than their sporadic counterparts (p = 0.08). Multivariable analysis demonstrated lower ACM risk in patients diagnosed with MEN1 (hazard ratio 0.35, 95% confidence interval 0.11–1.2, p = 0.09), further supporting the trend detected in the univariate analysis. In conclusion, our study demonstrates the distinct clinical profile of patients with MEN1-related PNET compared to sporadic disease and emphasizes the expertise required to accurately manage patients with PNET in this rare context. The cautious decision-making required before embarking on surgical intervention is further emphasized in this robust analysis of a large cancer database.

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder caused by pathogenic germline variants in the *MEN1* gene (11q13) encoding the menin protein [1]. The prevalence of MEN1 ranges between 1 and 10 in 100 000 people in the general population [2]. The syndrome is characterized by the occurrence

of primary hyperparathyroidism (PHPT) and pancreatic islet- and anterior pituitary tumors [3]. The most common manifestation of MEN1, occurring in almost all patients, is PHPT and is usually the earliest manifestation in patients, presenting before the 6th decade of life [4].

The reported prevalence for entero-pancreatic neuroendocrine tumors (NET) in MEN1 ranges between 30–80 % [5], while the rate of MEN1 among patients with pancreatic NET (PNET) varies depending on the functional status of the tumor, ranging between 3–15 % in nonfunctioning PNET, to 20–25 % in gastrin secreting PNETs [2]. The majority of MEN1-related PNET are gastrinomas, insulinomas, and nonfunctioning tumors [5]. Other less frequently detected PNET types in MEN1 include glucagonomas, vasoactive intestinal peptide secreting tumors, and somatostatinomas [5]. The reported prevalence of pituitary tumors among patients with MEN1 varies between 10 and 60 %, and it may be the first clinical manifestation in approximately 25 % of de-novo cases [6]. Microscopically, MEN1-related PNETs occur in 80–100 % of patients with MEN1. Hence they are often multiple, located throughout the pancreas but become symptomatic only in a minority of patients (0–13 %)[7]. Patients with MEN1 are prone to develop other neoplasms, including adrenal tumors, thyroid adenomas, thymic, gastric, and/or bronchial NET, brain meningiomas and ependymomas, skin lesions and smooth-muscle tumors, and also breast cancer [8, 9].

Diagnosis with MEN1 may be defined based on one of the following criteria: Clinical diagnosis, in the presence of two out of the three main MEN1-related manifestations (primary hyperparathyroidism, anterior pituitary tumor, and/or entero-pancreatic NET); Familial diagnosis, in the presence of one MEN1-related manifestation when at least one first-degree relative is also diagnosed with MEN1, or Genetic diagnosis, when a germline pathogenic variant is detected in the *MEN1* gene [5].

Patients with MEN1 have shorter longevity compared with the general population [10]. In the past, Zollinger–Ellison syndrome (ZES) was the major cause of death in MEN1, but proton-pump inhibitors practically eliminated the catastrophic manifestations of ZES, such as perforated ulcers and massive upper gastrointestinal bleeding. This led to MEN1-related PNET becoming the main cause of death in this syndrome [11, 12]. Yet, whether MEN1-related PNETs confer a higher mortality risk than their sporadic counterparts is still to be determined.

In the current work, we compared the mortality risk between sporadic and MEN1-related PNET and aimed to identify risk factors for mortality among patients with MEN1-related PNET to allow clinical identification of patients that may benefit from a more aggressive and early intervention.

Materials and Methods

This was a retrospective, population-based, case-control study based on the Surveillance, Epidemiology and End Results (SEER) database. The SEER database, maintained by the National Cancer Institute, provides cancer incidence and survival data from population-based registries, includes more than 3 million cases, and accounting for approximately 30 % of the United States population. In the current study, we analyzed the November 2018 update providing information for cases diagnosed between 2000 and 2016.

Data retrieved for the current analysis included patient demographics (age at diagnosis, gender, and ethnicity), tumor characteristics (stage, grade, and surgical intervention), and outcomes (survival since diagnosis and cause of death). The SEER database is publicly available, open for analysis by the scientific community, and patients' data are anonymized. Hence, institutional ethical approval was not required.

Cohort construction

The current analysis included patients documented in the SEER database, diagnosed with either pituitary adenomas or PNET of any type, either functional or non-functional. The diagnoses were sorted and identified based on the ICD-O-3 [13] histologic codes (**Table 1S**) and based on the NET anatomic site. Since diagnosis with pituitary adenoma and PNET defines MEN1, we identified patients with both diagnoses as those harboring MEN1-related PNET – the control group comprised of patients with PNET alone ('Sporadic PNET').

Statistical analysis

The analysis was performed on R Studio version 1.2.5001. Tumor grades were classified according to the SEER database definition, as the current definitions by the WHO for pancreatic neuroendocrine tumors grading have not been used during most of the study period and are not documented. Staging is reported based on the American Joint Cancer Classification (AJCC) 6th Edition [14] and according to the SEER staging definitions (localized, regional metastases, and distant metastases). Survival analysis was based on the SEER data and on the time since diagnosis until death or last follow-up. Continuous variables were compared using the Student's t-test, and categorical parameters were compared using the chi-square test. Continuous variables are presented as mean ± standard deviation (SD) unless stated otherwise, and categorical parameters are presented as n (%). Change in management efficacy over the study period was adjusted by defining the earliest year of diagnosis per group, and the latter year was set as a threshold for inclusion for both groups. Survival analysis was performed using the Kaplan–Meier method and compared by the log-rank test. Multivariable analysis was done using the proportional Cox regression analysis, controlling for covariates. A two-tailed p-value < 0.05 was considered statistically significant.

Results

The study cohort comprised of 569 PNETs cases (56.6 % male), 27 of them (4.7 %) have MEN1 based on clinical criteria. The mean age at diagnosis was 61.0 ± 13.2 years with a median of 62.0 [range 18.0, 89.0]. PNET were located at the head (27.2 %), body (13.5 %), or tail of the pancreas (31.5 %). Pancreatic-head NET were characterized by a higher grade (33.5 % well-differentiated in the pancreatic head vs. 49.2 % in body/tail PNET, p < 0.001) and stage (33.5 % localized in pancreatic head NET vs. 50.8 % in body/tail PNET, p = 0.001), and surgical intervention were performed less often for pancreatic head versus body/tail PNET (45.8 vs. 67.6 %, p < 0.001, respectively). Considering the higher rate of PNET multiplicity on MEN1, we compared patients with a single record of PNET to those with multiple PNET records. When comparing multiple vs. single events, neither age at diagnosis, gender, stage, grade or surgical

treatment were significantly different. However, a higher fraction of patients with multiple PNETs were of hispanic ancestry (28.6%) compared to their representation among those with a single PNET (8.9%, p = 0.009). The cohort characteristics and comparison between patients with sporadic vs. MEN1-related PNET are detailed in ▶ Table 1.

Univariate analysis – MEN1-related versus sporadic PNETs

Age at diagnosis with MEN1-related PNET was significantly younger than with sporadic PNET (49.2 ± 16.7 vs. 61.6 ± 12.8 years, respectively, p < 0.001). PNET pancreatic location, grade, and stage were comparable between the MEN1 and sporadic groups (▶ Table 1).

▶ **Table 1** Demographic and tumor characteristics of entire cohort.

	Overall	Sporadic	MEN1	p
n	569	542	27	
MEN1 n (%)	27 (4.7)	NA	NA	
Age (years)				
Mean (SD)	61.00 (13.24)	61.59 (12.78)	49.22 (16.72)	**<0.001**
Median (range)	62.00 (18.0, 89.0)	62.50 (22.0, 89.0)	54.0 (18.0, 72.0)	**<0.001**
Male sex n (%)	322 (56.6)	305 (56.3)	17 (63.0)	
Ethnicity n (%)				
Hispanic	55 (9.7)	51 (9.4)	4 (14.8)	0.627
Caucasian	416 (73.1)	400 (73.8)	16 (59.3)	**0.028**
African American	59 (10.4)	53 (9.8)	6 (22.2)	0.553
Asian or Pacific Islander	35 (6.2)	35 (6.5)	0 (0.0)	0.15
Other	4 (0.7)	3 (0.6)	1 (3.7)	0.081
Location in pancreas n (%)				0.812
Head	155 (27.2)	147 (27.1)	8 (29.6)	
Body	77 (13.5)	75 (13.8)	2 (7.4)	
Tail	179 (31.5)	170 (31.4)	9 (33.3)	
Other parts	28 (4.9)	28 (5.2)	0 (0.0)	
Overlapping lesions	42 (7.4)	39 (7.2)	3 (11.1)	
Unknown	88 (15.5)	83 (15.3)	5 (18.5)	
Grade n (%)				0.605
I (Well differentiated)	231 (40.6)	217 (40.0)	14 (51.9)	
II (Moderately differentiated)	66 (11.6)	62 (11.4)	4 (14.8)	
III (Poorly differentiated)	23 (4.0)	22 (4.1)	1 (3.7)	
IV (Undifferentiated anaplastic)	12 (2.1)	12 (2.2)	0 (0.0)	
Unknown	237 (41.7)	229 (42.3)	8 (29.6)	
Stage n (%)				0.257
Localized	235 (41.3)	221 (40.8)	14 (51.9)	
Regional	121 (21.3)	114 (21.0)	7 (25.9)	
Distant	184 (32.3)	180 (33.2)	4 (14.8)	
Unknown	29 (5.1)	27 (5.0)	2 (7.4)	
Stage AJCC n (%)				0.558
I	112 (19.7)	106 (19.6)	6 (22.2)	
II	260 (45.7)	246 (45.4)	14 (51.9)	
III	70 (12.3)	66 (12.2)	4 (14.8)	
IV	127 (22.3)	124 (22.9)	3 (11.1)	
Single event n (%)	548 (96.3)	522 (96.3)	26 (96.3)	1
Surgery performed n (%)	327 (57.5)	310 (57.2)	17 (63.0)	0.695

MEN1: Multiple endocrine neoplasia type 1. NA: Not applicable.

In terms of ethnic composition, a trend toward more patients of African American ancestry was found among patients with MEN1 (22.2%) versus sporadic PNET (9.8%, p=0.08). Nevertheless, when comparing patients of African American ancestry to other patients, other patient and tumor characteristics were comparable.
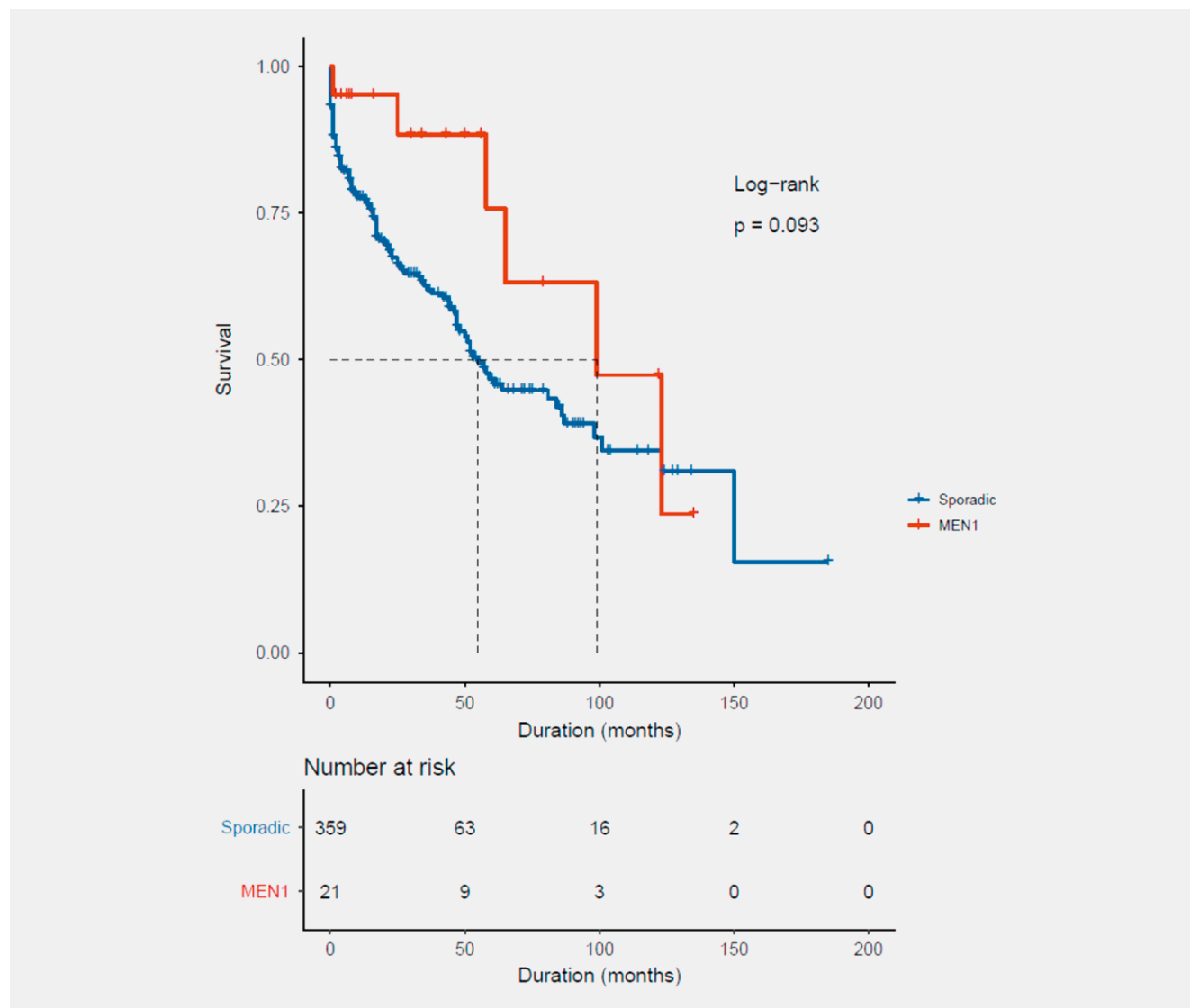
All-cause mortality

We did not find a significantly different risk for all-cause mortality (ACM) in our analysis. However, a trend for lower ACM was found for patients with MEN1-related vs. sporadic PNET (Log-rank test, p=0.09, ▶ Fig. 1) and especially among those with nonfunctioning PNET (p=0.07). A similar trend was found among patients with advanced disease, both based on the SEER staging system and based on AJCC staging, with lower ACM risk found in patients with MEN1-related versus sporadic PNET (p=0.08 for both comparisons, ▶ Fig. 2). Comparison between patients with MEN1-related and sporadic PNET, demonstrated a trend for lower ACM in those that did not undergo surgical intervention (p=0.08, ▶ Fig. 3).

Multivariable analysis

We performed a multivariable Cox-regression analysis, adjusting for patient and tumor characteristics. In the adjusted survival analysis, age at diagnosis, tumor grade, and stage were all independently associated with increased risk for all-cause mortality (▶ Fig. 4). Again, a trend for lower ACM was found, even after adjusting for the covariates, in MEN1-related versus sporadic PNET (Hazard ratio 0.351, 95% confidence interval 0.105–1.17, p=0.07).

Discussion

In this study, we aimed to assess tumor and patient-related factors associated with increased risk for all-cause mortality in patients with sporadic and MEN1-related PNETs based on the SEER database. Our analysis demonstrated that patients with MEN1-related PNET are diagnoses at a younger age, as expected. The MEN1 group included a higher percentage of patients of African American ancestry compared with the sporadic PNET group. Although our com-

▶ Fig. 1 Kaplan–Meier analysis, comparing all-cause mortality risk between patients with MEN1-related and sporadic pancreatic neuroendocrine tumors. MEN1: Multiple endocrine neoplasia type 1.
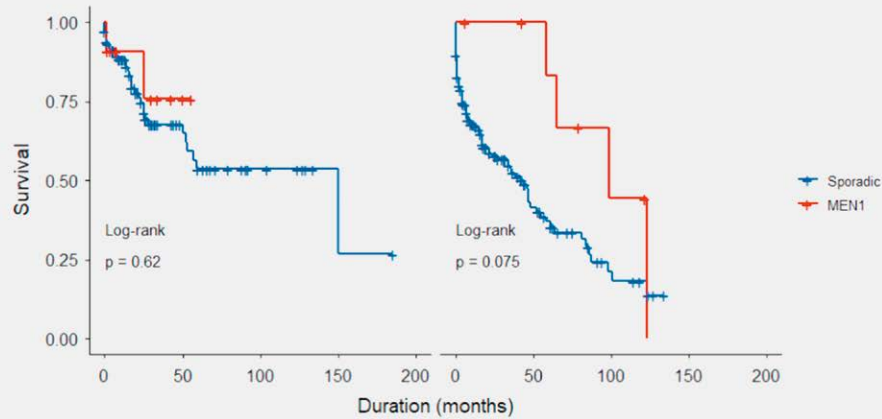
▶ **Fig. 2** Kaplan–Meier analysis, comparing all-cause mortality risk between patients with MEN1-related and sporadic pancreatic neuroendocrine tumors – stratified by disease stage (localized disease – left, advanced disease – right). MEN1: Multiple endocrine neoplasia type 1.
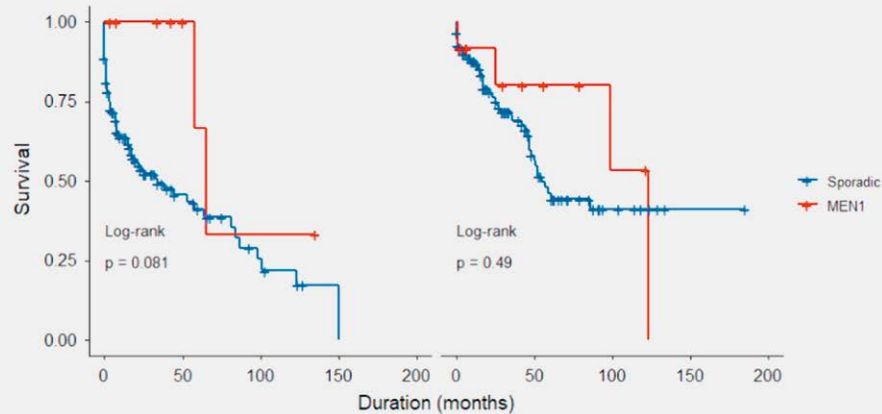
▶ **Fig. 3** Kaplan–Meier analysis, comparing all-cause mortality risk between patients with MEN1-related and sporadic pancreatic neuroendocrine tumors – stratified to patients in which surgical intervention was performed (right) or not (left). MEN1: Multiple endocrine neoplasia type 1.

parative survival analysis did not reach statistical significance, the MEN1 group had a consistent trend for lower all-cause mortality risk across most analyses, including patients with advanced disease (AJCC stage III/IV). Importantly, among patients that did not undergo surgical resection of their tumor, those with MEN1-related PNET had better outcome compared to those with sporadic PNET. The trend for lower mortality risk in MEN1-related PNET was also found in the multivariable analysis.

Our finding that patients with MEN1-related PNET were diagnosed at a younger age compared to those with sporadic PNET is expected as has been previously reported [7, 15, 16] and provides support for our cohort validity. Similarly, the increased risk for ACM by higher grade and stage in the multivariable analysis supports our study results.

We found that among patients that were followed expectantly (with no surgical intervention), those with MEN1-related PNET had lower ACM rates than sporadic PNET. A possible explanation is the low risk of small MEN1-related PNET to advance over time, as shown

in previous studies of the Dutch and French MEN1 cohorts [17]. Our results support the conservative, non-invasive approach in patients with MEN1-related NET in the lack of clear benefit. Previously, the French research group of MEN1 showed that MEN1 patients with small NF-PNETS who undergone pancreatic surgery did not differ significantly in tumor progression compared to conservative treatment, and therefore suggested that surgery is not beneficial in this population [18].

Our study demonstrates once more that NETs in the context of hereditary syndromes are distinct from their sporadic counterparts. The genetic predisposition leads to clinical differences that should be translated into syndrome-specific clinical management. Specifically, we demonstrated that in patients with MEN1-related PNET, the risk for all-cause mortality may be lower compared to patients with sporadic PNET. Our analyses did not reach statistical significance, explained by the small sample size, but were consistent over several subgroup analyses and in the multivariable model.
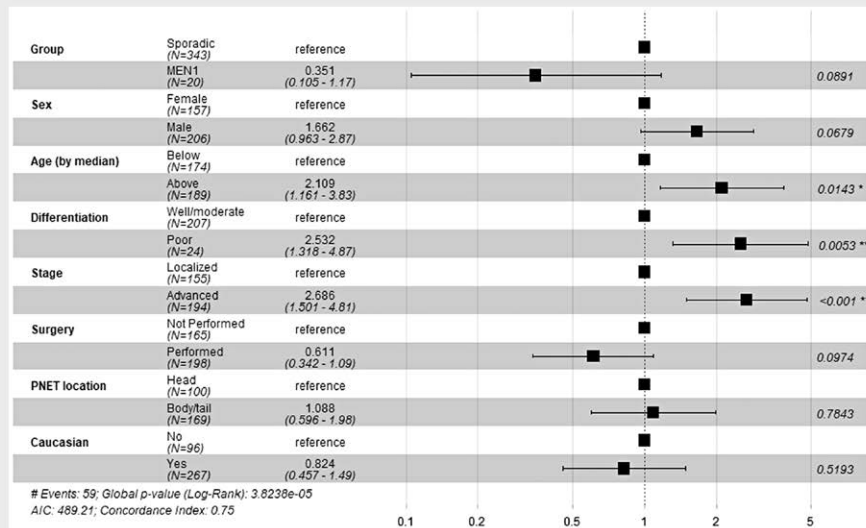
▶ **Fig. 4** Multivariable analysis for all-cause mortality in patients with sporadic and MEN1-related pancreatic neuroendocrine tumors. MEN1: Multiple endocrine neoplasia type 1.

Hence, we advise choosing a cautious approach when considering surgical intervention in patients with MEN1-related PNET.

This study is based on one of the largest cancer databases available. The SEER database is a population-based cohort, representing the US population in an unbiased way. The data available enabled us to perform a robust multivariable analysis and to define the differences in the risk for mortality between MEN1-related and sporadic PNET. Our study had several unavoidable limitations that should be considered when interpreting our results. First, this study was a retrospective study, with all the inherent limitations and biases of this methodology. Second, our study may inaccurately represent the general MEN1 population for three reasons: 1. Small sample size, 2. Possible inclusion of MEN1 phenocopies manifesting with PA and PNET, such as MEN4, and 3. Defining MEN1 patients based on PNET and PA co-occurrence and not based on parathyroid adenomas or family history, which are not reported in the SEER database. Third, since *MEN1* genotype is not reported in the SEER database, the possible association between *MEN1* mutation status and life expectancy could not be assessed [19]. Finally, we could not adjust for other comorbidities that may affect mortality risk.

In conclusion, based on a large cancer database, and while considering the above mentioned limitations we provide further validation to the less aggressive behavior of MEN1-related PNET, that while did not reach statistical significance, support previous studies, and may reflect on our clinical approach with patients suffering from this unique and rare syndrome.

Conflict of Interest

The authors declare that they have no conflict of interest.

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