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Survival and Incidence Patterns of Pancreatic Neuroendocrine Tumors Over the Last 2 Decades: A SEER Database Analysis

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Abstract

Background: Pancreatic neuroendocrine tumors (pNETs) are rare cancers with outcomes determined by multiple factors including grade, stage, and clinical presentation. In this study, we aimed to determine the prognosis of patients with pNETs using a large population-based database.

Materials and Methods: In this population-based study, we identified patients with pNETs from the SEER 18 registry (2000-2016) using a combination of ICD-O-3 and histology codes. We calculated age-adjusted incidence rates using SEER*Stat 8.3.5. In addition, we analyzed overall survival (OS) using the Kaplan-Meier method, and investigated prognostic factors using a multivariable Cox proportional hazards model.

Results: A total of 8944 pNETs patients were identified. Annual incidence rates increased from 0.27 to 1.00 per 100 000. This was largely explained by an increase in number of patients diagnosed with localized disease in more recent years (2012-2016). Median OS was 68 months (95% CI [64, 73]) and 5-year OS rates in localized, regional, and metastatic disease were 83%, 67%, and 28%, respectively. There was a significant improvement in OS for patients diagnosed between 2009 and 2016 (median OS 85 months) compared with those diagnosed between 2000 and 2008 (median OS 46 months) (HR 0.66; 95% CI [0.62, 0.70]). This improvement in OS was consistent across all stages.

Conclusions and Relevance: This study shows a steady increase pNETs incidence with notable stage migration to earlier stages in recent years. This increase in incidence is accompanied by a significant improvement in survival across different disease stages.

Key words: neuroendocrine tumors; SEER; incidence; pancreatic tumors.

Implications for Practice
In this study, the investigators find that the incidence of pNETs has increased over the last 2 decades. Significant number of these cancers are being diagnosed in earlier stages. This increase in incidence is associated with improvement in survival across all stages.

Introduction

Pancreatic neuroendocrine tumors (pNET) are rare neoplasms that comprise less than 2% of all pancreatic malignancies. These tumors are thought to arise from islet cells of the pancreas and are known to have different outcomes based on grade, stage, and clinical presentation.[1-3] The overall incidence of neuroendocrine neoplasms has been steadily increasing along with improvement in overall survival (OS) over time[4]. [5,6] However, it is not clear whether this increase in incidence and survival applies to pNET after approval of newer agents such as everolimus and sunitinib. Therefore, a more focused and updated look at the incidence and mortality trends of pNET

across different stages would be helpful in delineating such patterns which can help in better understanding of the disease.

In this study, we aimed to use the Surveillance, Epidemiology, and End Results (SEER) cancer registry to study trends in the incidence and mortality of pNET in the US over the last 2 decades.

Materials and Methods

Data source

Data on patients diagnosed with pNETs between 2000 and 2016 were drawn from the SEER 18 registry.[7]

Study Population

Patients diagnosed with pNETs between 2000 and 2016 whose diagnosis did not rely on autopsy or death certificates were included in this analysis. Patients were identified using a combination of topographical codes (International Classification of Diseases for Oncology, 3rd Edition, ICD-O-3: C25.0, C25.1, C25.2, C25.3, C25.4, C25.7, C25.8, and C25.9) and histology codes (8150, 8151, 8152, 8153, 8155, 8240, 8241, and 8246).

Outcomes and Statistical Analysis

Using SEER*Stat 8.3.5, age-adjusted incidence rates were calculated and plotted by year of diagnosis (in 1-year increments with/without stratified stage status, race, and age at diagnosis). Patient demographics and clinical characteristics were summarized as count (percentage) by groups of year of diagnosis (2000-2018, 2009-2016) including sex, age at diagnosis race, grade (I, II, III), stage and surgery on primary tumor. Grades III and IV were combined into a single category[4] and are henceforth referred to as grade III. Using SAS 9.4, OS was compared across strata defined by stage (localized, regional, distant), grade (I, II, III), year of diagnosis (2000 to 2008, 2009 to 2016), and with/without surgery via 2-sided log-rank tests with a nominal significance level of α =.05. Overall survival was plotted via the Kaplan-Meier method for the full sample and by strata for each of these prognostic factors. Median OS and 5-year OS rates were also calculated for the full sample and by strata for each of these prognostic factors. Finally, univariate and multivariable Cox proportional hazards regression models were applied to investigate the association between OS and the factors including year of diagnosis (2000 to 2008, 2009 to 2016, and in 1-year increments), age at diagnosis (in 5-year increments), stage (localized, regional, distant), grade (I, II, III), sex (male, female), race (White, Black, other), functional status and surgery on the primary tumor (yes, no). All tests were 2-sided, and *P*-values of <.05 were considered significant.

Results

Baseline Characteristics

Between 2000 and 2016, 8944 patients with pNETs were identified (Table 1). Most patients were White (7108/ 8898, 79.88%), 45 years or older (7803/ 8944, 87.24%), and with non-metastatic disease at diagnosis (4794/8606, 55.71%). Tumor grade was available for 5148 (57.56%) of the 8944 patients, with most having grade I tumors (3547/ 5148, 68.90%).

Incidence Rates and Trends Over Time

The overall incidence during the study period was 0.61 per 100 000 person-years. Age-adjusted incidence rate was comparable between Black patients and White patients at 0.69 and 0.61 per 100 000, respectively (Supplementary Fig.

Table 1. Baseline characteristics of the included patients

Characteristic	Year of diagnosis		Total (*N* = 8944)
	2000 to 2008 (*N* = 2804)	2009 to 2016 (*N* = 6140)	
Female sex	1275 (45.5%)	2725 (44.4%)	4000 (44.7%)
Age at diagnosis			
44 years or younger	405 (14.4%)	736 (12.0%)	1141 (12.8%)
45 to 64 years	1322 (47.1%)	2708 (44.1%)	4030 (45.1%)
65 years or older	1077 (38.4%)	2696 (43.9%)	3773 (42.2%)
Race			
White	2298 (82.1%)	4810 (78.9%)	7108 (79.9%)
Black	313 (11.2%)	737 (12.1%)	1050 (11.8%)
Other	187 (6.7%)	553 (9.1%)	740 (8.3%)
Missing	6	40	46
Grade			
I	574 (52.0%)	2973 (73.5%)	3547 (68.9%)
II	254 (23.0%)	637 (15.7%)	891 (17.3%)
III	275 (24.9%)	435 (10.8%)	710 (13.8%)
Unknown	1701	2095	3796
Stage			
Localized	531 (20.2%)	2567 (43.0%)	3098 (36.0%)
Regional	549 (20.9%)	1147 (19.2%)	1696 (19.7%)
Distant	1552 (59.0%)	2260 (37.8%)	3812 (44.3%)
Unstaged or unknown	172	166	338
Surgery on primary tumor			
Yes	1165 (41.8%)	3253 (53.2%)	4418 (49.7%)
No	1622 (58.2%)	2857 (46.8%)	4479 (50.3%)
Missing	17	30	47

Patient demographic and disease characteristics by year of diagnosis.

S1). Diagnosis with pNETs peaked among 70- to 74-year-old patients, with an incidence rate of 2.45 per 100 000 (Supplementary Fig. S2). Annual incidence rates increased over the study period from 0.27 to 1.00 per 100 000 (Fig. 1). The increase in incidence over the study period can largely be explained by a significant increase in the number of patients diagnosed with localized disease in recent years (ie, 2012 to 2016) (Fig. 2).

Median overall survival (mOS) for the entire cohort was 68 months (95% CI [64, 73]), and 5-year OS rates localized, regional, and metastatic disease were 83.19% (SE = 0.86%), 67.36% (SE = 1.31%), and 28.13% (SE = 0.79%), respectively (Fig. 3a). The 5-year OS rates in grade I, grade II, and grade III tumors were 77.33% (SE = 0.87%), 63.06% (SE = 1.92%), and 20.04% (SE = 1.60%), respectively (Fig. 3b).The 5-year OS rates for different stage/grade groups
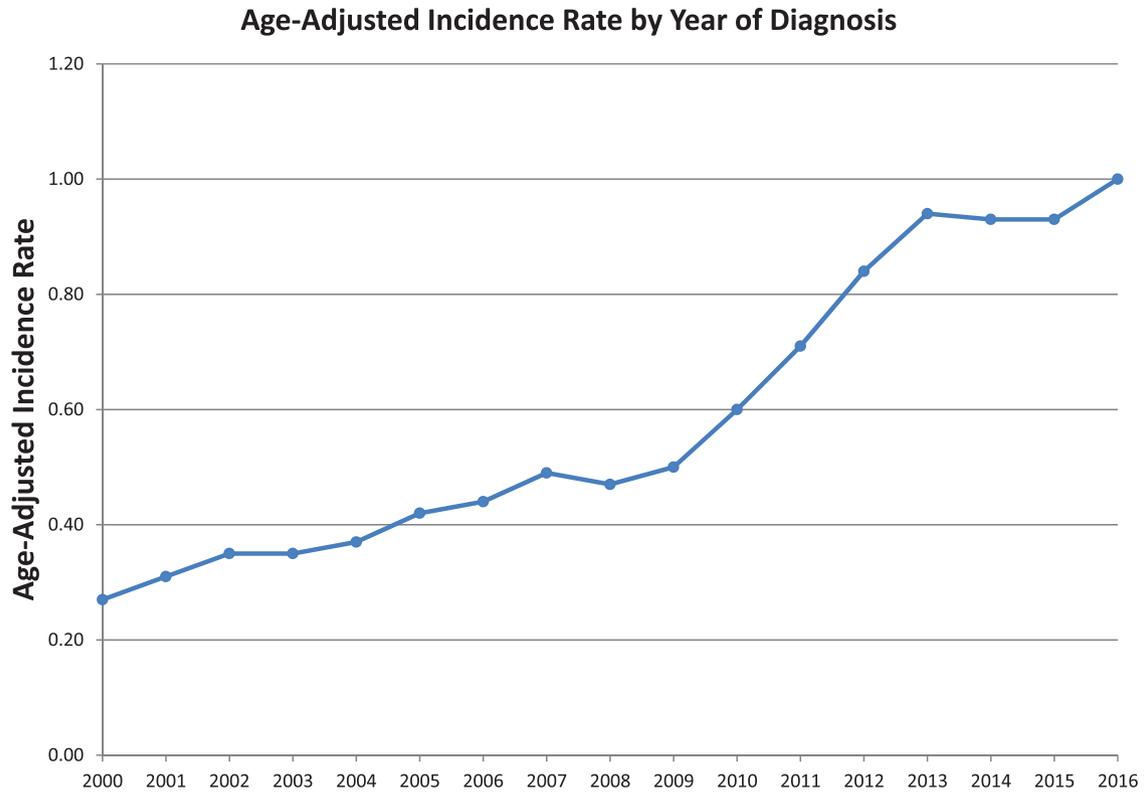

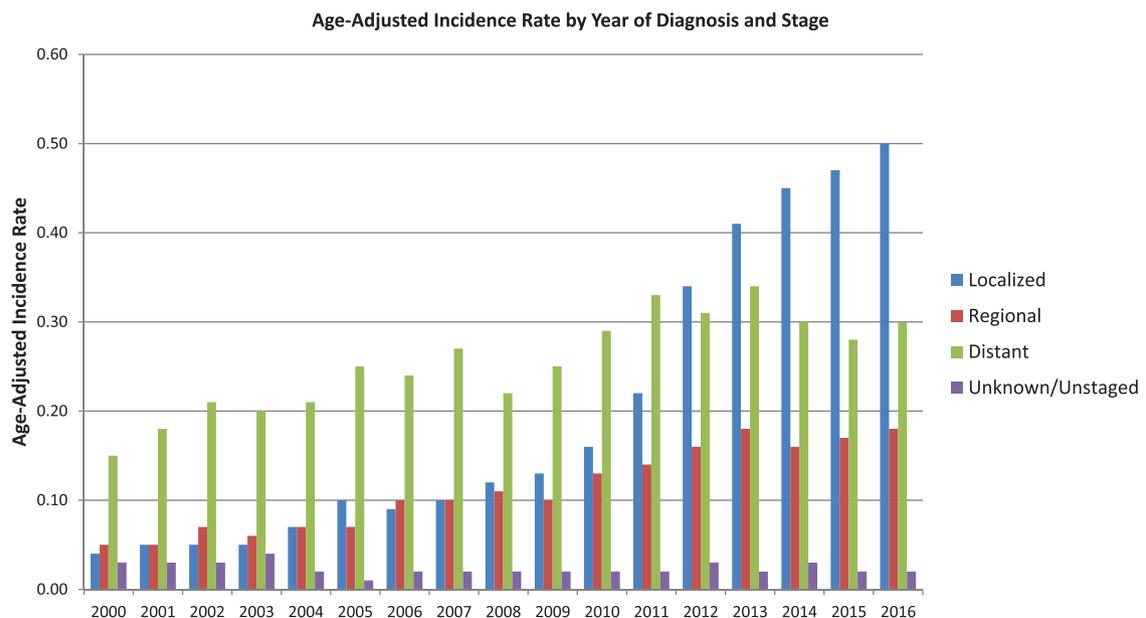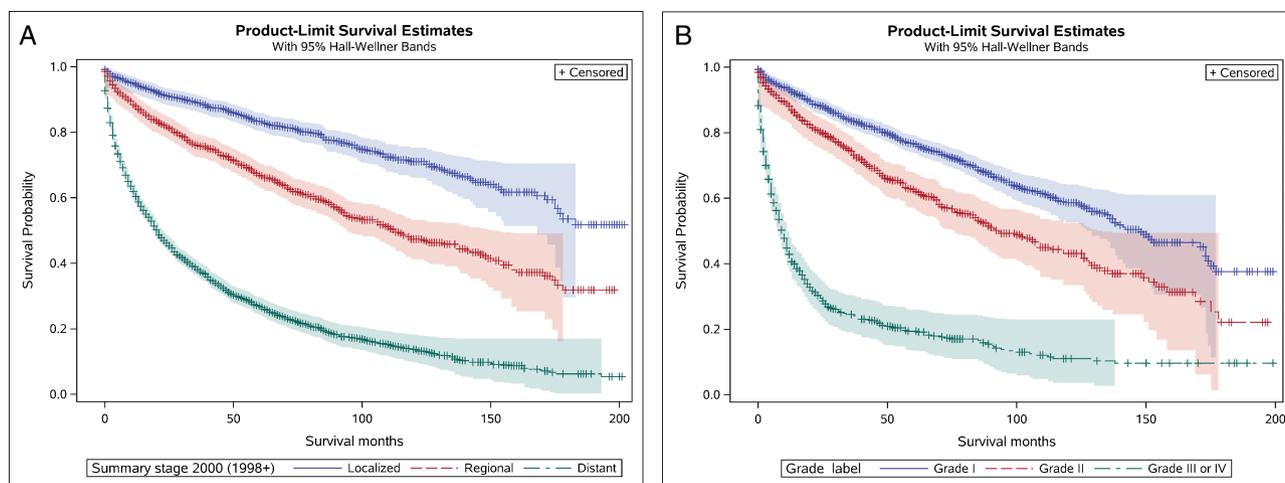**Figure 1.** Age-adjusted incidence rate by year of diagnosis.

Figure 2. Age-adjusted incidence rate by year of diagnosis and stage.

Figure 3. (A) Kaplan-Meier curve for overall survival in patients with localized, regional, and distant pNETs. (B) Kaplan-Meier curve for overall survival in patients with grade I, grade II, and grade III pNETs.

were: 87.28%, 79.69%, and 46.24% for localized grade I, grade II, and grade III, respectively; 80.99%, 72.49%, and 38.19%, for regional grade I, grade II, and grade III, respectively; 51.03%, 45.16%, and 12.37% for metastatic grade I, grade II, and grade II, respectively.

There was a significant improvement in OS for patients diagnosed between 2009 and 2016 (mOS = 85 months) compared with those diagnosed between 2000 and 2008 (mOS = 46 months) (log-rank test: $\chi^2(1)$ = 154.95, P <.001; univariate Cox proportional hazards: HR = 0.66, 95% CI [0.62, 0.70]), which was seen across all stages (Fig. 4). Patients with metastatic grade I/II (or unknown) disease who underwent surgery experienced significantly longer OS (mOS = 84 months) compared with those who did not undergo surgery (mOS = 18 months) (log-rank test: $\chi^2(1)$ = 354.15, P <.001; univariate Cox proportional hazards: HR = 0.31, 95% CI [0.28, 0.36]) (Supplementary Fig. S3). In the univariate Cox proportional hazards regression models, more recent year of diagnosis (ie, 2009—2016), younger age at diagnosis, localized disease, lower grade, female sex, race other than White or Black, and surgery on the primary tumor were all associated with longer OS. In the multivariable Cox proportional hazards regression model, more recent year of diagnosis, younger age at diagnosis, localized disease, lower grade, female sex, and surgery on the primary tumor were associated with longer OS (Table 2). In contrast, race was not significantly associated with OS.

Discussion

Different population-based studies have shown an increase in NET incidence over time with a 6.4-fold increase between 1973 and 2012.[4,8] This same trend was reflected in our study with an overall increase in annual incidence of pNETs from 0.27 to 1.00 per 100 000, from 2000—2016. This increase in incidence was mainly represented by a higher proportion of early stage disease (localized) in more recent years. Although not possible to evaluate using SEER data, it is likely that a substantial proportion of patients diagnosed at an earlier stage were diagnosed incidentally in the absence of symptoms related to the malignancy. With increased use of cross-sectional imaging as an evaluation tool for a variety of clinical

conditions, we have observed an increasing number of incidental pNET diagnoses in the clinic, often at earlier stages. In addition to the increase in incidence, we saw significantly better survival in pNET patients diagnosed between 2009 and 2016 compared with those diagnosed between 2000 and 2008. While some of this can be explained by more patients diagnosed at earlier stages, we found that this survival benefit was consistent across all stages.

Our data suggest a complex epidemiologic signature with increase in incidence and decrease in mortality, which could be attributed to either increase in true cancer occurrence or increased diagnosis of early stage disease.[9] When we discuss any large database, we must acknowledge the Will Rogers phenomenon, or stage migration.[10] The increased use of cross-sectional imaging along with the improvement in imaging modalities with somatostatin receptor imaging probably explain this phenomenon in pNETs. In addition, it is important to note that the increased incidence in grade I cancers over time may also have contributed to the decreased mortality.

In addition to stage migration, the improvement in survival seen in our study was also probably a result of better treatment strategies as the improvement in survival in recent years was seen across all stages including advanced stage (ie, metastatic disease). Over the last 15 years, multiple treatment options have been developed in pNET. In addition to the somatostatin analog lanreotide,[11] everolimus was approved by the US Food and Drug Administration (US FDA) based on a phase III trial showing favorable outcomes in patients receiving everolimus compared to placebo.[12] Similarly, sunitinib was approved based on progression-free survival of 11.4 months in patients receiving sunitinib compared with 5.5 months in those receiving placebo.[13] Other more recent therapeutic developments are expected to further increase this survival in pNET such as the combination of capecitabine/temozolomide[14] and peptide receptor radionuclide therapy (Lu 177).[15,16] Although the largest trial studying PRRT (NETTER-1) excluded pNETs, both prospective and retrospective studies showed promising efficacy in pNET leading to FDA approval of Lutathera for grades I and II gastroenteropancreatic NETs.[15] In addition to the abovementioned treatment strategies, recent translational work has led to a better understanding of the genetic
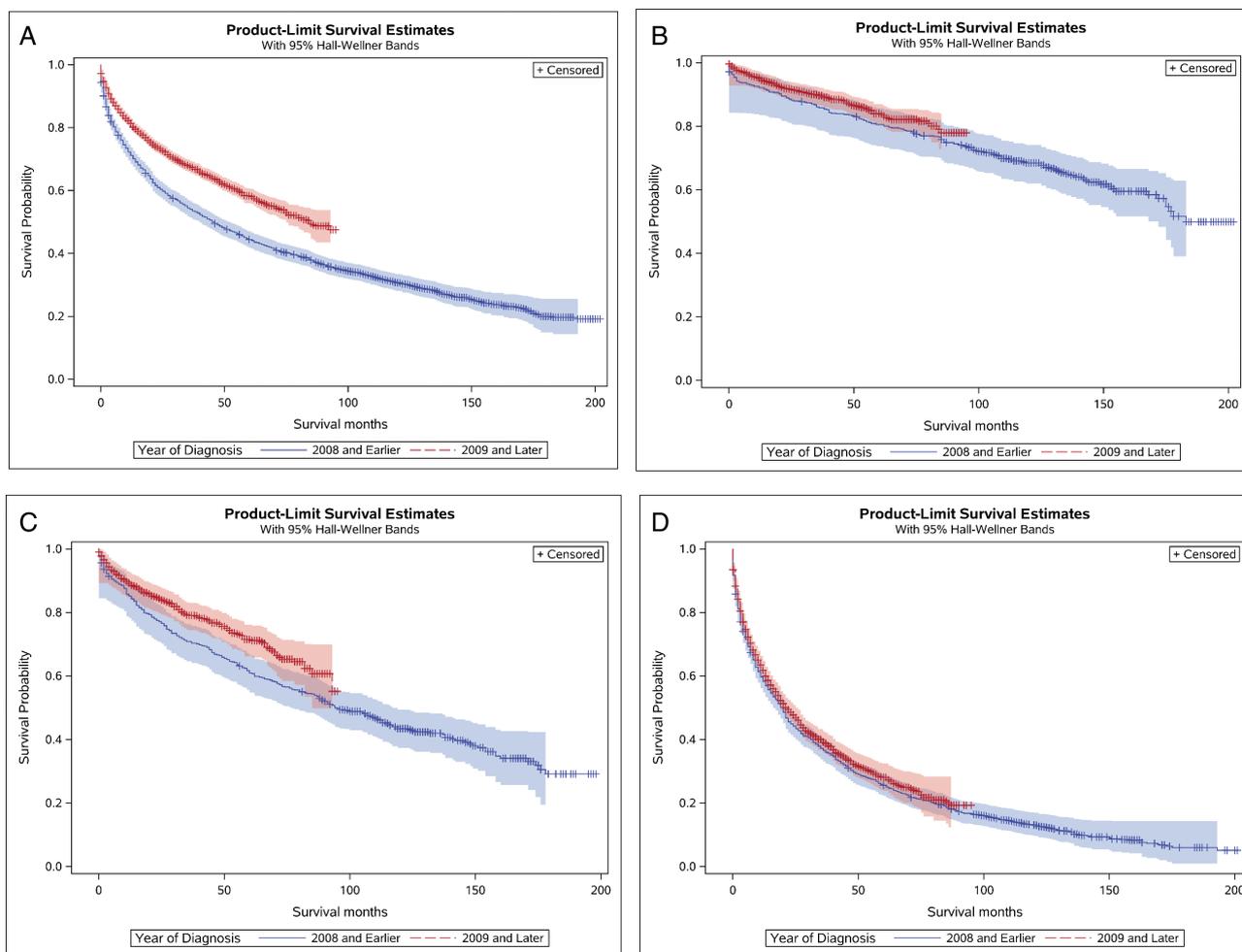
Figure 4. Kaplan-Meier curve for overall survival by year of diagnosis for: (A) all stages; (B) localized stage; (C) regional stage; (D) metastatic stage.

Table 2. Multivariable cox proportional hazards regression for cases diagnosed between 2000 and 2016.

Prognostic factor	Reference group	*P*-value	Hazard ratio
Year of diagnosis (1-year increments)		<.001	0.97 (0.96, 0.98)
Age at diagnosis (5-year increments)		<.001	1.15 (1.12, 1.17)
SEER stage—regional	Localized	<.001	1.62 (1.37, 1.91)
SEER stage—distant	Localized	<.001	2.78 (2.38, 3.25)
Grade—grade II	Grade I	.007	1.21 (1.05, 1.39)
Grade—grade III	Grade I	<.001	3.47 (3.06, 3.93)
Sex—female	Male	.001	0.84 (0.76, 0.94)
Race—black	White	.16	1.12 (0.96, 1.32)
Race—other	White	.31	0.90 (0.74, 1.10)
Functional status—functional	Nonfunctional	.85	0.96 (0.63, 1.47)
Surgery	No surgery	<.001	0.35 (0.31, 0.40)

and molecular pathways in pNETs, paving the way for future therapeutic developments.[17]

Current guidelines recommend surveillance imaging for a total of 10 years in patients with pNET after complete resection, with considering discussion with patients after that regarding continuing or ceasing surveillance.[18] In our study, we found an apparent continuous decrease in survival

after 10 years in low-grade pNETs. Of course, the current analysis did not delineate whether these deaths are secondary to pNETs, as it has been shown in different studies that non-NET causes of deaths are responsible for significant number of deaths in low-grade NETs.[19,20] Our study is not without limitations that are mainly related to its observational nature and reliance on the SEER database. One

limitation of the SEER database is that it classifies neuro-endocrine neoplasms into 4 grades: grade I, well differentiated; grade II, moderately differentiated; grade III, poorly differentiated; and grade IV, undifferentiated or anaplastic. To better resemble the recent WHO classifications, we combined grade III and IV into one category as was performed by others.[4] In addition, the SEER database does not provide granular data regarding Ki-67 index and differentiation. Another limitation is the lack of information of patients' comorbidities along with other details related to the functional status of the pNETs. Therefore, the identification of functional tumors using SEER data is unreliable. Despite the limitations of the SEER database, we believe that it provides the most recent and comprehensive data for examining incidence and survival trends of pNETs over time.

Conclusion

There has been a steady increase in the incidence of pNETs with notable stage migration as most patients are diagnosed in early stages of disease in recent years. Additionally, this increase in incidence is accompanied by a significant improvement in survival across different disease stages.

Conflict of Interest

Jason Starr: Tersera, Natera, Advanced Accelerated Applications, Pfizer, Taiho, Ipsen (C/A); **Thorvardur R. Halfdanarson**: Ipsen, Advanced Accelerator Applications, Curium, TerSera, Crinetics, ITM, Terumo (C/A), Advanced Accelerator Applications, Thermo Fisher Scientific, Basilea, Turnstone Biologics (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Author Contributions

Conception/design: M.B.S., G.L.M., T.O., J.S., H.G., S.P.C., T.H., T.R.H. Provision of study material/patients: M.B.S., G.L.M., T.R.H. Collection and/or assembly of data: M.B.S., G.L.M., T.O., J.S., H.G., S.P.C., T.H., T.R.H. Data analysis and interpretation: G.L.M., L.M. Manuscript writing: M.B.S., G.L.M., T.O., J.S., H.G., S.P.C., T.H., T.R.H. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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