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ORIGINAL ARTICLE

Life expectancy in pancreatic neuroendocrine cancer

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Summary
Background: The prognoses widely reported for pancreatic cancer reflect the very poor survival associated with the most common histological type, exocrine adenocarcinoma. We calculated life expectancies for patients with less common pancreatic neuroendocrine tumors (PNETs), and also for the subsets of these patients who survive 1 and 5 years post-diagnosis, all of which carry a significantly better prognosis. Results for 1- and 5-year PNET survivors appear not to have been previously reported, nor have life expectancies (average long-term survival times) been given.
Methods: We identified 5287 cases of PNET in the SEER US national database, 1973—2013. The Kaplan—Meier estimator was used to compute empirical survival probabilities and median survival times for functioning ($n = 279$) and non-functioning PNET ($n = 5008$) cases. The Cox proportional hazards regression model was used to examine univariate associations of survival with covariates including patient age, sex, race, cancer stage, tumor grade, surgical treatment, and calendar year. A multivariate multiplicative hazard Poisson regression model estimated mortality rates for all combinations of the covariates. The rates were used to construct actuarial life tables, which gave life expectancies for male and female patients according to age, cancer stage, tumor grade, histology (functioning versus non-functioning), surgical treatment status, and time since diagnosis. These life expectancies were compared with age- and sex-specific figures from the US general population.
Results: Life expectancy in PNET is lower than that of the US general population and varies significantly according to patient age, cancer stage, tumor grade, mode of treatment, and time since diagnosis. For example, it is near normal for persons aged 70 and older who undergo surgical resection of localized well-differentiated (i.e., grade I) tumors. By contrast, persons with metastatic high-grade tumors not amenable to surgery have life expectancies of only 1 to 4 years depending on patient age. Functioning PNETs were associated with somewhat lower mortality than non-functioning within the first few years after diagnosis, though no major differences were observed long-term. Positive factors for survival were younger age, localized stage,

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low tumor grade, and surgical treatment. Survival improved over the 1973—2013 study period: on average mortality rates fell by 1.2% per year after controlling for changes in the patient population. Life expectancy increased markedly with time since diagnosis: those surviving 1 and 5 years post-diagnosis had longer additional life expectancies.

Conclusions: Life expectancies of patients with PNETs may be markedly reduced from normal, but even in the worst cases their prognoses remain significantly better than that of patients with the more common pancreatic adenocarcinomas. In some very favorable cases, the life expectancy is near-normal, especially amongst 1- and 5-year survivors. This information can be used to counsel patients.

Introduction

Pancreatic cancer is relatively rare, with approximately 13 new cases and 12 deaths per 100,000 population per year in the United States [1]. Overall survival prognosis is exceptionally poor, with only approximately 8% of patients surviving 5 years post-diagnosis [1]. Unlike in many other forms of cancer, there do not appear to have been significant improvements in survival over the past few decades [1].

However, the outcome statistics are dominated by exocrine adenocarcinomas, which account for approximately 90% of cases [2]. While patients with this histological type often have median survival times of less than 1 year [2], prognoses for those with the less common pancreatic neuroendocrine tumors (PNETs) appear to be significantly better [2—5]. For example, the 2008 study of Yao et al. reported a median survival time of 5 years from diagnosis [3].

The seminal work of Fesinmeyer et al. [2] together with further research by others [3—7] identified various risk factors related to survival in PNETs. Their results, however, were limited to relatively short-term survival probabilities (up to 5 years post-diagnosis) and were stratified by only one or two risk factors at a time, which has only limited utility in providing accurate prognoses for individual patients. For example, Keutgen et al. [8,9] reported univariate survival curves and medians based on age, grade, location, and other factors, but did not provide results specific to any two factors or a combination of factors.

More recent studies have investigated recurrence and survival based on revised WHO 2010 and 2017 diagnostic criteria and various clinical markers [10—15]. Insufficient time has passed, however, to investigate long-term survival based on refined clinical characteristics (such as Ki67 proliferative index, mitosis rate, lymph node ratio, p53 and rb1) [11].

Further, none of these works contained either life expectancies (the total average survival time) or conditional figures (e.g., for those who survive 1 year post-diagnosis). That is, to our knowledge, there have been no studies that specifically computed life expectancies with comparison to the general population. Nor have there been any studies reporting the subsequent survival of PNET patients who had already survived 1 or 5 years post-diagnosis.

The present study updates and expands on previous work, especially Keutgen et al. [8,9] by developing a multivariate prediction model that simultaneously accounts for patient age and sex, cancer stage, tumor grade and histology, and surgical treatment status. Using this model, we examine trends in survival over time, controlling for these factors. Primarily, we use the model to obtain current life expectancy (i.e. mean survival time) estimates from the time of diagnosis, and also conditional life expectancy estimates for 1- and 5-year survivors. The latter may be particularly relevant and helpful to patients who have survived the initial treatment and are then naturally concerned about their future prospects. Finally, we compare our results to normal figures for the US general population, to highlight to what extent survival in functional and non-functional PNET is diminished.

Materials and methods

Data source and cohort selection

The Surveillance, Epidemiology, and End Results (SEER) database, managed and maintained by the National Cancer Institute (NCI), is the largest source of information on cancer incidence and survival in the United States. The registries that provide patient information for SEER represent approximately 28% of the US population (based on the 2010 census). We queried the 2015 edition of the SEER database which includes over 8.2 million cases diagnosed between 1973 and 2013 in the United States [16].

We included all adult (age $\geq$ 18 years) cases of arising in primary site 25 (pancreas) or 24.1 (ampulla of Vater) with known patient age, proven malignancy, and documented follow-up time and vital status. Our primary analysis was restricted to histologic codes for functioning PNET (8151 insulinoma; 8152 glucagonoma; 8153 gastrinoma; 8155 VIPoma; 8156 somatostatinoma) and non-functioning PNET (8013 large cell neuroendocrine carcinoma; 8150 islet cell carcinoma; 8246 neuroendocrine carcinoma). These are the same histological codes used by Keutgen et al. [8,9] with one exception: Cases with code 8154 were excluded because they indicate mixed endocrine/exocrine histology and were shown by Keutgen et al. [8] to have a significantly worse prognosis. We also excluded persons with prior histories of other cancers. The final selection included 5287 cases (5008 non-functioning, and 279 functioning). For comparative purposes, we also examined survival for other-

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wise similar patients with pancreatic adenocarcinoma (code 8140; $n = 87136$).

Outcome

The primary outcome of interest was survival time (i.e., time from diagnosis until death from any cause). The survival times of persons not matched to death records were right-censored.

Covariates/risk factors

The potential explanatory covariates examined were sex, age at diagnosis, race (white vs. other), histology group (non-functioning vs. functioning), cancer stage (localized, regional, distant), tumor grade (I—II vs. III—IV), surgical treatment status (yes/no), and diagnosis year. The SEER database includes multiple staging variables, each of which covers a different range of data with some overlap. These include the old SEER Historic Staging [localized (stages I and II), regional (III), distant (IV)] as well more recent AJCC classifications based on TNM. In the present analysis, we worked with LRD staging, as this allowed for consistent definitions across the entire study period. We return to this issue in the discussion. Data on all covariates were at least 95% complete (i.e., non-missing) for the overall case selection with the exception of tumor grade (56% missing).

Data analysis

Empirical survival probabilities at 1, 5, and 10 years after diagnosis as well as median survival times were estimated with the Kaplan—Meier method [17]. Log rank tests [17] were used to assess unadjusted differences in survival by histological groupings; a P-value < 0.05 was considered statistically significant. Empirical conditional survival probabilities were calculated in the usual way. For example, the conditional probability of survival to the 10th year after diagnosis for persons who had already survived 5 years was calculated by dividing the 10-year survival probability by the 5-year survival probability.

Univariate associations of each covariate with survival were examined using Cox proportional hazards regression models [17]. For this analysis, age at diagnosis was categorized into groups (18—49, 50—59, 60—69, 70—79, and 80+) and year of diagnosis according to decade. Each level of these and other categorical variables were input to the model as indicator variables. Likelihood ratio tests [18] (compared with the null model) were used to test associations with survival. For each level of each covariate, the proportional hazards assumption was assessed using graphical methods (i.e., plots of smoothed scaled Schoenfeld residuals as a function of follow-up time) and with the Grambsch—Therneau global test [19].

Each covariate was also included in a multivariate multiplicative hazard Poisson regression model that allowed the hazard ratios for certain covariates to change with time since diagnosis (i.e., non-proportional hazards) [20]. The functional forms of time-dependent effects were informed by the univariate graphical assessments discussed above. Interactions between covariates were examined. Model selection was based in part on Akaike's Information Criterion [18] together with biologically plausible global constraints on certain parameter values. As an example of the latter, we rejected models that predicted mortality rates lower than those of age- and sex-matched persons in the US general population [21].

Life expectancies (i.e., mean survival times) from diagnosis for various combinations of covariates were calculated based on the schedule of age-specific mortality rates from the multivariate model. In brief, the mortality rates at each age following diagnosis (up to age 109 years) were used as the inputs to standard actuarial life tables with 1-year intervals, and life expectancies were obtained from the ''e(x)'' column of the resulting life tables [22]. It may be noted that conditional life expectancies at 1 or 5 years after diagnosis are also naturally reported in the ''e(x)'' column of the same actuarial life tables. Life expectancies were compared with those of the age- and sex-specific US general population.

All data management and analyses were completed in SAS 9.4 and R 3.0.

Results

Patient characteristics

Characteristics of the 5287 PNET cases are presented in Table 1. The mean age at diagnosis was 58 years and 54% were male. The large majority of cases (95%) were non-functioning histological types. Some 54% of all cases were diagnosed as distant stage and surgery was performed in 52% overall. Tumor grade was missing in 56% of cases, but amongst those with known grade the majority were well-differentiated grade I.

Because non-functioning histologies made up the large majority of cases, the covariate distributions observed within this subgroup were very similar to the overall distributions noted above. By contrast, persons with functioning histologies were diagnosed at younger ages (mean 45), were somewhat less likely to have distant stage cancer (43%), and were more likely to undergo surgery (56%).

There were a number of significant associations between cancer stage and other covariates (not shown in Table 1). For example, amongst cases with non-missing data the proportion of high-grade (III—IV) tumors in persons with distant stage disease was higher than in persons with regional or localized disease (32% vs. 20% vs. 5%). Conversely, some 57% of high-grade tumors were diagnosed at a distant stage whereas only 9% were diagnosed at the localized stage. Surgical resection was less likely in persons with distant stage disease than in those with regional or localized disease (24% vs. 78% vs. 83%). Similarly, low-grade tumors were more likely than high-grade tumors to have been treated surgically. The likelihood of surgical resection also declined with advancing age at diagnosis ($P < 0.0001$). Localized cases were equally split between men and women (51% male), while men were slightly over-represented in regional (52%) and distant (56%) cases. There was no association between patient age and cancer stage ($P = 0.12$). Finally, there was a trend toward diagnosis at earlier stages in more recent years ($P < 0.0001$).

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Table 1 Patient characteristics. All figures are column percentages except sample sizes.

	Overall	PNET	
		Non-functioning	Functioning
Total sample size	5287	5008	279
Male	54	55	45
Age at diagnosis			
18—49	27	27	37
50—59	25	25	22
60—69	25	25	21
70—79	17	17	16
80+	6	6	4
Race			
White	81	81	79
Other	19	19	21
LRD stage			
Localized	21	21	24
Regional	20	20	25
Distant	54	55	43
Missing	5	5	8
AJCCSummary stage			
I	13	14	8
II	11	11	3
III	2	2	0
IV	19	30	5
Missing	45	43	84
Grade			
1	26	26	19
2	9	10	6
3	7	7	1
4	2	2	1
Missing	56	55	73
Surgery			
Yes	52	53	56
No	46	46	42
Missing	2	1	2
Year of diagnosis			
1973—79	3	3	3
1980—89	5	5	15
1990—99	12	12	26
2000—09	46	46	40
2010—13	33	34	16

PNET: pancreatic neuroendocrine tumors; LRD: localized, regional, distant.

Empirical survival by histology

Empirical estimates of median survival time and probabilities of survival to 1, 5, and 10 years after diagnosis by histology are shown in Table 2. As can be seen, the overall/unadjusted median survival from diagnosis of PNET was 4.1 additional years (95% CI: 3.9—4.4). This is considerably longer than the 6-month median for the more common pancreatic adenocarcinoma (log rank $P < 0.0001$). Survival was significantly longer for functioning PNET than for non-functioning (median of 7.3 vs. 4.0; log rank $P = 0.0002$). Sample sizes were too small to make meaningful inferences regarding differences in survival according to specific functioning PNET subtype (e.g., insulinomas vs. glucagonomas vs. gastrinomas).

Median survival times of 1-year survivors were markedly higher than those from time of diagnosis. For PNET overall, this was 5.9 additional years (95% CI: 5.4—6.3) or equivalently 6.9 years from the time of diagnosis (cf. 4.1). The statistically significant differences in survival by histologic type noted above were still apparent in 1-year survivors.

Median survival of 5-year survivors was longer still, namely 9.8 additional years (95% CI: 8.7—10.4) for PNET overall; equivalently, this is 14.8 years from the time of diagnosis. The 5-year conditional survival was similar for both functioning and non-functioning (median 9.6 vs 10.2; log rank $P = 0.198$). These were significantly longer than the corresponding conditional median survival for exocrine adenocarcinoma (7.4; log rank $P < 0.0001$).

Univariate analyses of covariates on survival

All covariates considered here had statistically significant univariate associations with survival time (Table 3). The largest unadjusted hazard ratios (HR) were those related to cancer stage and tumor grade. For example, unadjusted mortality rates for distant stage disease were 6.5 (95% CI: 5.6—7.5) times those for localized disease. The HR for grade IV versus grade I tumors was 6.2 (95% CI: 4.9—7.8). Surgery was associated with a univariate HR of 0.2 (95% CI: 0.2—0.3). As would be expected, mortality rates increased with advancing age. Men had slightly higher mortality than women (HR = 1.1, 95% CI: 1.0—1.2), and whites slightly higher than other races (HR = 1.1, 95% CI: 1.0—1.2).

Multivariate modeling

The multivariate modeling exercise confirmed that most of the univariate associations remained statistically significant after adjustment for other covariates. One exception was race; this covariate was therefore dropped from the model. In order to capture the time-dependent effects of many of the covariates, the data were converted from a wide to long time-dependent format and mortality rates were thus modeled as an explicit function of time since diagnosis and its interactions with other covariates (e.g., age, stage, grade, histology, surgery, and calendar year). The effects of current/attained patient age and calendar year were modeled using time-dependent covariates rather than the baseline values of age and year at diagnosis. Though equivalent models can be constructed regardless of this choice, the former was chosen because it resulted in a more parsimonious and easily interpretable model. The effects of time since diagnosis, age, and calendar year were modeled using linear splines.

The final Poisson regression model (Table 4) included 32 coefficients [an intercept, 15 main effect terms (of which 9 were linear spline functions of time since diagnosis, age, and calendar year), 6 interaction effect terms, and 10 time-dependent effects]; the AIC (based on the Poisson likelihood function) was 19,620. Due to the complexity of the model, merely reporting the magnitude of the hazard ratios for the main terms is not sufficient to explain

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Table 2 Kaplan–Meier (unadjusted) survival and conditional survival by histology.

Group	Persons	Median additional years (95% CI)	1-year	5-year	10-year
From time of diagnosis					
All PNET	5287	4.1 (3.9–4.4)	77%	46%	31%
Non-functioning	5008	4.0 (3.8–4.3)	76%	45%	29%
Functioning	279	7.3 (5.6–10.7)	88%	60%	46%
Exocrine adenocarcinoma	87,136	0.5 (0.5–0.5)	27%	4%	3%
For 1-year survivors					
All PNET	3695	5.9 (5.4–6.3)	100%	60%	40%
Non-functioning	3460	5.8 (5.3–6.2)	100%	59%	38%
Functioning	235	9.4 (6.9–11.4)	100%	68%	52%
Exocrine adenocarcinoma	21,757	0.7 (0.7–0.8)	100%	16%	10%
For 5-year survivors					
All PNET	1366	9.8 (8.7–10.4)	100%	100%	67%
Non-functioning	1237	9.6 (8.4–10.4)	100%	100%	65%
Functioning	129	10.3 (7.5–18.4)	100%	100%	77%
Exocrine adenocarcinoma	2325	7.4 (6.9–8.3)	100%	100%	60%

PNET: pancreatic neuroendocrine tumors.

the fully adjusted effects of the covariates on mortality, which were entirely consistent with those found in the univariate analyses. For example, distant stage cancers with high-grade tumors were associated with much shorter survival than localized well-differentiated low-grade tumors. Similarly, surgery remained a marker for longer survival even with multivariate adjustment for stage, grade, and other factors.

Examination of interactions between covariates indicated that relative differences in mortality rates were generally greater amongst lower risk groups than in higher risk groups. For example, the female sex advantage (universally found in the general population) was only apparent in persons with well-differentiated tumors, i.e., of grades I or II. Similarly the relative increase in mortality with advancing age was greater in persons with localized disease and was smaller in persons with distant disease, likely reflecting the fact that mortality rates in distant stage disease are already quite high even at young ages. Finally, the interaction term for distant stage cancers and high-grade tumors indicated somewhat lower mortality than would be expected under a multiplicative main terms model.

Survival improved over the study period: on average mortality rates fell by 2.7% per year from 1970–1989, increased by about 3.4% per year during years 1990–1999 and then decreased again by 2.6% from 2000 to 2013. Overall, mortality fell by 1.2% per year over the study period.

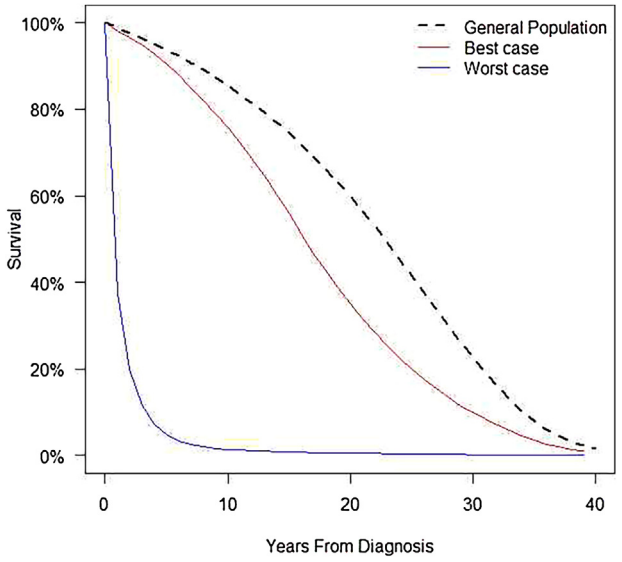

Figure 1 Survival curves for 60-year-old men with non-functioning pancreatic neuroendocrine tumors (PNET). General population: median survival time 23 years; life expectancy 22. Best case: localized stage, low-grade, surgical resection; median 16 years, life expectancy 17. Worst case: distant stage, high-grade, no surgical resection; median survival < 1 year; life expectancy 1.

Survival curves and life expectancies for particular patterns of covariates

Using the final multivariate model, period survival curves and life expectancies keyed to calendar year 2013, which is most recent year represented in the SEER national database, were computed. Fig. 1 provides fitted survival curves for 60-year-old men with non-functioning tumors; this includes a ''best case'' (specific to localized stage, grade I or II, treated surgically), and a ''worst case'' (distant stage, grade III or IV, not treated surgically). Fig. 1 also compares these curves with the empirical survival for 60-year-old men in the US general population [21,22].

Tables 5a and 5b provide life expectancies from time of diagnosis and also at 1- and 5-years post-diagnosis for men and women, respectively. For example, in males age 50 with localized stage, grades I–II, non-functioning, treated surgically, the life expectancy is approximately 23 additional years, a reduction of 7 years from normal. For those currently aged 50, but who had survived 1 year post-diagnosis (having been diagnosed at age 49), the life expectancy is also 23 additional years. For those also age 50, but who had

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Table 3 Univariate hazard ratios (HR) from Cox proportional hazards (PH) regression models.

Covariate	HR	*P*	Violation of PH?
Male	1.1	0.0006	No
White	1.1	0.2558	No
Age			Yes
18—49	ref	—	
50—59	1.2	0.0001	
60—69	1.7	< 0.0001	
70—79	2.3	< 0.0001	
80+	3.6	< 0.0001	
Stage (LRD)			Yes
Localized	ref	—	
Regional	2.3	< 0.0001	
Distant	6.5	< 0.0001	
Missing	3.4	< 0.0001	
Stage (AJCC)		—	Yes
AJCC I	ref	< 0.0001	
AJCC II	2.3	< 0.0001	
AJCC III	6.1	< 0.0001	
AJCC IV	10.0	< 0.0001	
Missing	6.1		
Grade		—	Yes
I	ref	< 0.0001	
II	1.8	< 0.0001	
III	5.3	< 0.0001	
IV	6.2	< 0.0001	
Missing	2.9		
Histology		—	Yes
Non-functioning	ref	< 0.0001	
PNET: functioning	0.7		
Surgery		—	Yes
No	ref	< 0.0001	
Yes	0.2	0.0016	
Missing	0.6		
Year of diagnosis		—	Yes
1973—79	ref	0.3397	
1980—89	0.9	0.1124	
1990—99	0.7	< 0.0001	
2000—09	0.6	< 0.0001	
2010—13	0.5	< 0.0001	

PNET: pancreatic neuroendocrine tumors; LRD: localized, regional, distant.

survived 5 years post-diagnosis (diagnosed at age 45), the life expectancy is 23 additional years.

By contrast, the difference between life expectancy of newly diagnosed patients and the conditional life expectancy of 1- and 5-year survivors is striking for the more unfavourable cases. Consider males age 50 with non-functioning PNET, distant metastasis, no surgery. For those recently diagnosed the life expectancy is 6 years, but the fraction who survive 1 year post-diagnosis have a higher life expectancy, 7 years, and those who have survived 5 years have a higher still, 10 years.

As can be seen, even the most favorable cases — i.e., localized well-differentiated tumors that are amenable to surgical resection — are still associated with a 6—8 year reduction from the general population life expectancy at age 50 and a 2—3-year reduction at age 70. As might be expected, the most unfavourable cases — i.e., metastatic high-grade tumors that are not amenable to surgery — are associated with life expectancies of only 2—4 years if diagnosed at age 50 and only 1—2 years if diagnosed at age 70.

Discussion

As would be expected, we found PNET to be associated with reduced life expectancy, with an overall empirical median survival time of 4.1 years from diagnosis. Though this is considerably lower than the median survival time for persons of similar age and sex in US the general population, it is roughly 8 times longer than the 6-month median survival time for the more common pancreatic adenocarcinomas.

The present study indicates that survival prognosis varies dramatically according to patient characteristics, ranging from about 1 year in a 70-year-old with a recent diagnosis of high-grade metastatic cancer to 26—27 additional years for a 50-year-old woman with a recent diagnosis of localized low-grade cancer treated surgically.

The relatively high life expectancies for persons with localized disease that is amenable to surgery underscore the importance of early detection. Unfortunately, such favorable cases were the minority. In the present study, roughly 75% of cases were diagnosed only after significant cancer spread (i.e., regional or distant stage) and only about 50% overall were treated surgically. The data did, however, indicate a trend towards earlier detection in more recent years, which may well lead to longer survival in patients with PNETs overall.

Conversely, it should be recognized that even the most favorable combinations of risk factors considered here were still associated with some reduction from normal life expectancy when diagnosed in relatively young adults. The reduction was some 7—8 years in 50-year-old men and women but was only 2—3 years at age 70. Equivalently, these figures are about 80% of the normal age- and sex-specific US general population life expectancies.

The prognoses for persons with unfavorable risk factors — i.e., distant stage, high-grade, not amenable to surgery — was much poorer, with life expectancies on the order of 1—4 years from diagnosis depending on patient age. However, the conditional life expectancies of 5-year survivors in these same groups were 5 to 10 additional years, which again indicates that the excess mortality risk decreases with time. This almost certainly reflects the healthy survivor effect, but whether it can be attributable to a particular fraction of ''cured'' patients cannot be determined from the SEER data, which unfortunately does not collect well-documented follow-up data on remission or recurrence.

The life expectancies reported here are necessarily based on and subject to the predictive performance of the multivariate model. The inferences from this model are consistent with the those presented in the seminal work of Fesinmeyer et al. [2] and other more recent studies from Halfdanarson et al. [4,5], Yao et al. [3], and Keutgen et al. [8,9]. The estimates from the present study, however, are

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Table 4 Multiplicative hazard Poisson regression model.

Covariate	Coefficient	HR	*P*
Intercept	−4.466	—	< 0.0001
Linear spline terms			
Years since diagnosis	0.484	1.623	0.0119
Linear spline at year 1	−0.504	0.604	0.0119
Linear spline at year 5	−0.070	0.932	0.0848
Linear spline at year 10	0.029	1.029	0.4767
Age-18 (years)	0.027	1.027	0.0002
Linear spline at age 55	0.024	1.024	< 0.0001
Calendar year-1973	−0.027	0.973	0.0058
Linear spline at year 1990	0.034	1.034	0.0454
Linear spline at year 2000	−0.026	0.974	0.0365
Other main effect terms			
Functioning PNET	−0.032	0.969	0.8565
Regional stage	1.980	7.241	< 0.0001
Distant stage	2.843	17.174	< 0.0001
Unknown stage	1.636	5.133	0.0032
Surgical resection	−0.004	0.996	0.9887
Unknown surgical status	−0.520	0.594	0.4478
Interaction effect terms			
Age × Regional stage	−0.023	0.978	0.0004
Age × Distant stage	−0.030	0.971	< 0.0001
Age × Unknown stage	−0.013	0.987	0.0905
Age × Surgical resection	0.004	1.004	0.3058
Male × Low-grade	0.280	1.323	0.0014
Distant stage × High-grade	−0.194	0.823	0.1396
Time-dependent effects			
Age × Years since diagnosis < 1	0.013	1.013	< 0.0001
Age × Years since diagnosis; linear spline beyond year 2	0.000	1.000	0.3394
Functioning PNET; linear spline up to year 10	−0.037	0.963	0.1148
Regional stage; linear spline up to year 10	0.046	1.047	0.0585
Distant stage; linear spline up to year 10	0.067	1.069	0.0066
Unknown stage; linear spline up to year 10	0.000	1.000	0.9967
High-grade; linear spline up to year 15	0.103	1.108	< 0.0001
Unknown-grade; linear spline up to year 15	0.035	1.035	< 0.0001
Surgical resection; linear spline up to year 15	−0.093	0.911	< 0.0001
Unknown surgical status; linear spline up to year 15	0.025	1.025	0.6303

PNET: pancreatic neuroendocrine tumors.

likely to be considerably more precise in light of the much larger and more recent sample. Further, our use of more sophisticated statistical modeling techniques allowed us to estimate survival for much more refined risk strata and to consider possible interactions of covariates and time-dependent effects.

As discussed above, adverse risk factors included older age, more advanced cancer stage, and higher tumor grade. Surgical resection, which is the gold standard treatment in pancreatic cancer generally, was a strong positive factor for survival. However, the differences in life expectancy by surgical treatment status in the present study must not be interpreted as pure causal effects, as our analysis suggested surgically treated patients are subject to some healthy selection bias [9]. Persons who do not receive surgery may well have additional health risks that would compromise their ability to undergo surgery or may have tumors in specific locations that are not amenable to surgical resection [9]. Race was not a significant factor after adjustment for these, which suggests that any apparent differences according to race may largely be attributable to the timing of detection. Similarly, functioning versus non-functioning had similar survival. The small but significant survival advantage for functional PNETs during the first few years after diagnosis may be partially explained by earlier detection following symptoms associated with changes in hormone production.

Our analysis appears to be the first to examine trends in survival across calendar years. We found that overall (i.e., unadjusted for other factors) mortality declined by 1.6% per year, equivalent to a 48% total reduction from 1973 to 2013. This appears to be at least partially explained by a trend towards detection and diagnosis of PNET at earlier stages. After adjustment for covariates, including cancer stage, the trend was still significant but was modestly attenuated to an average improvement of only 1.2% per year or

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Table 5a Life expectancies for men with pancreatic neuroendocrine cancer, 2013. The three figures in each cell are for persons of the stated age at one of three times: recently diagnosed/1-year survivor/5-year survivor.

Age	GP	Grades 1–2					
		Non-functioning PNET			Functioning PNET		
		Localized	Regional	Distant	Localized	Regional	Distant
50[a]	30	23/23/23	16/16/16	11/11/12	24/24/23	18/18/17	13/13/12
55[a]	26	20/20/19	15/15/14	10/10/10	21/20/20	16/16/15	12/12/11
60[a]	22	17/17/16	13/13/13	9/9/9	18/18/17	14/14/13	11/11/10
65[a]	18	15/14/14	11/11/11	8/8/8	15/15/14	13/12/11	10/10/9
70[a]	15	12/12/11	10/10/9	7/8/7	13/13/12	11/11/10	9/9/8
50[b]	30	21/21/23	12/12/15	6/7/10	22/23/24	14/14/16	8/9/11
55[b]	26	18/18/19	10/11/13	5/6/9	19/19/20	12/13/14	7/8/10
60[b]	22	14/15/16	8/9/11	5/5/8	16/16/17	10/11/12	6/7/8
65[b]	18	12/12/13	7/8/10	4/5/7	13/13/14	9/9/10	5/6/7
70[b]	15	9/10/11	6/7/8	3/4/6	11/11/11	7/8/9	5/5/6
Age	GP	Grades 3–4					
		Non-functioning PNET			Functioning PNET		
		Localized	Regional	Distant	Localized	Regional	Distant
50[a]	30	21/21/23	11/12/16	8/9/12	22/23/24	14/14/17	10/11/13
55[a]	26	17/18/19	10/11/13	7/8/11	19/19/20	12/12/14	9/9/12
60[a]	22	14/15/16	8/9/11	6/6/9	16/16/17	10/11/12	7/8/10
65[a]	18	11/12/13	7/7/9	5/5/8	13/13/14	8/9/10	6/7/9
70[a]	15	9/9/10	5/6/8	4/5/7	10/11/11	7/8/9	5/6/7
50[b]	30	15/17/22	4/6/13	2/3/9	18/19/23	7/8/14	4/5/10
55[b]	26	12/13/18	4/5/11	2/3/8	14/15/19	6/7/12	3/4/9
60[b]	22	9/10/14	3/4/9	2/2/7	11/12/15	4/6/10	3/4/8
65[b]	18	6/7/11	2/3/7	1/2/5	8/9/12	3/5/8	2/3/6
70[b]	15	4/5/9	2/3/6	1/2/5	6/7/9	3/4/7	2/3/5

PNET: pancreatic neuroendocrine tumors.
[a] Surgery.
[b] No surgery.

a 38% total reduction from 1973 to 2013. The latter can be interpreted as trends in mortality independent of changes in the patient mix. These undoubtedly partially reflect broader trends of improvement in the general population during the same period, but it is conceivable that advances in medical treatments are responsible for many of the gains. Unfortunately SEER does not contain detailed data on the use of chemotherapy and we therefore cannot test this hypothesis directly.

The present work also appears to be the first to report life expectancies (average survival times) in PNET calculated over the lifetime. Other studies have reported 5-, 10-, or even 20-year survival probabilities, but not life expectancies. Nor have prior works reported the associated survival figures for persons in the general population, so that comparisons could be made. Finally, this is the first study, to our knowledge, to report survival for those who have survived 1 or 5 years post-diagnosis. The latter is especially of interest to the ever-increasing number of patients who have had successful initial treatment, and are thus interested in long-term planning.

Limitations

The use of SEER's localized, regional, distant (LRD) staging classification is crude by comparison with the more refined AJCC staging systems based on TNM, and more recent WHO 2010 and 2017 divisions (PNET G1, G2, NEC). We chose to work with the simpler LRD system for three reasons. Firstly, it was much more complete (i.e., only 5% missing cf. AJCC 45% cf. no data in SEER using WHO 2017). Secondly, it allowed for a consistent staging classification, which is important when assessing trends in survival over time. Thirdly, the AJCC staging criteria for PNETs changed significantly from the 6th to 7th editions, making interpretation of results more complex. Finally, by using an older historical measure we obtained longer follow-up, which was necessary for the detailed calculations performed here; notably, we require a sufficient sample size of 5-year survivors in order to assess their subsequent life expectancy, and also long-term follow-up to fully capture the delayed excess mortality risk due to either recurrence or the sequellae of treatment.

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Table 5b Life expectancies for women with pancreatic neuroendocrine cancer, 2013. The three figures in each cell are for persons of the stated age at one of three times: recently diagnosed/1-year survivor/5-year survivor.

Age	GP	Grades 1—2					
		Non-functioning PNET			Functioning PNET		
		Localized	Regional	Distant	Localized	Regional	Distant
50[a]	34	26/26/26	20/20/20	14/14/14	27/27/26	21/21/20	16/16/15
55[a]	29	23/22/22	17/17/17	13/13/13	23/23/23	19/19/18	14/14/14
60[a]	25	19/19/19	15/15/15	11/12/12	20/20/19	17/16/16	13/13/12
65[a]	21	17/17/16	14/14/13	10/10/10	18/17/16	15/15/14	12/12/11
70[a]	17	14/14/13	12/12/11	9/9/9	15/15/14	13/13/12	10/10/10
50[b]	34	24/25/26	15/16/19	9/10/13	26/26/27	17/18/20	11/12/14
55[b]	29	21/21/22	13/14/17	8/9/12	22/22/23	15/16/17	10/10/13
60[b]	25	17/18/19	11/12/14	7/8/10	19/19/19	13/14/15	8/9/11
65[b]	21	14/15/16	9/10/12	6/7/9	16/16/16	11/12/13	7/8/10
70[b]	17	11/12/13	8/9/10	5/6/8	13/13/13	10/10/11	6/7/8
Age	GP	Grades 3—4					
		Non-functioning PNET			Functioning PNET		
		Localized	Regional	Distant	Localized	Regional	Distant
50[a]	34	21/22/24	12/13/16	8/9/12	23/23/24	14/14/17	10/11/13
55[a]	29	18/18/20	10/11/14	7/8/11	19/19/20	12/13/14	9/9/12
60[a]	25	14/15/16	8/9/11	6/6/9	16/16/17	10/11/12	7/8/10
65[a]	21	11/12/13	7/7/10	5/6/8	13/13/14	8/9/10	6/7/9
70[a]	17	9/9/10	5/6/8	4/5/7	10/11/11	7/8/9	5/6/7
50[b]	34	15/17/22	5/6/13	2/3/9	18/19/23	7/8/14	4/5/10
55[b]	29	12/14/19	4/5/11	2/3/8	14/16/20	6/7/12	3/4/9
60[b]	25	9/10/15	3/4/9	2/2/7	11/12/16	4/6/10	3/4/8
65[b]	21	6/8/12	2/3/7	1/2/6	8/9/12	3/5/8	2/3/6
70[b]	17	4/6/9	2/3/6	1/2/5	6/7/10	3/4/7	2/3/5

PNET: pancreatic neuroendocrine tumors.
[a] Surgery.
[b] No surgery.

As noted previously, SEER does not contain direct information on patient symptoms and our analysis therefore could not examine whether tumor-related symptoms were associated with patient survival. Our classification of PNETs by histological type followed the same classifications used in earlier work [8,9]. Indeed, while certain symptoms are characteristic of specific functional histological types (e.g., hypoglycemia caused by insulinoma), such symptoms are not universal. Similarly, non-functional types may either present with or without symptoms such as diarrhea, indigestion, or abdominal pain. While our analyses indicated short-term survival of persons with functional histological types was somewhat better that that of persons with non-functional types, further research is necessary to elucidate how the presence of symptoms might affect time to detection and subsequent survival.

A further limitation of the present work is that stratification by treatment was limited to surgery and did not include the use of radiation or chemotherapy, the latter of which has only recently been introduced to SEER. Finally, the estimates of conditional life expectancy of 1- and 5-year survivors do not specifically account for long-term status in remission or cancer recurrence; this is an inherent limitation of the SEER database, which unfortunately does not include clinical follow-up data. Instead, our conditional life expectancy estimates serve as a broad guide to survival typical at 1 and 5 years after diagnosis. The conditional estimates are pessimistic for persons known to be in remission and optimistic for those whose cancer has recurred. For some patients with favorable characteristics at diagnosis and who are known to have been in continuous remission up to 5-years post-diagnosis and treatment, life expectancy may well be near normal, though the data are not sufficient to estimate this precisely. Indeed, further research that utilizes clinical follow-up data to assess these issues would be valuable for the continually growing population of cancer survivors. We hope that the results presented, especially life expectancies and conditional survival figures, while possibly crude and dated, will nevertheless encourage future researchers to use contemporary clinical distinctions to produce updated figures in the years to come.

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Conclusion

Life expectancies of patients with pancreatic neuroendocrine tumors are generally lower than general population figures, but even in the worst cases their prognoses remain significantly better than that of patients with the more common pancreatic adenocarcinomas. In some very favorable cases, the life expectancy is near-normal, especially amongst 1- and 5-year survivors. These results underscore the importance of early detection and treatment in improving outcomes overall.

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Disclosure of interest

The authors declare that they have no competing interest.

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References

[1] National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer stat facts: pancreatic cancer. [Available at https://seer.cancer.gov/statfacts/html/npancreas.html. Accessed March 9, 2018].
[2] Fesinmeyer MD, Austin MA, Li CI, De Roos AJ, Bowen DJ. Differences in survival by histologic type of pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2005;14:1766—73.
[3] Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after ''carcinoid'': epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063—72.
[4] Halfdanarson TR, Rubin J, Farnell MB, Grant CS, Petersen GM. Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors. Endocr Relat Cancer 2008;15:409—27.
[5] Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol 2008;19:1727—33.
[6] Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97:934—59.
[7] Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin North Am 2011;40:1—18.
[8] Keutgen XM, Nilubol N, Kebebew E. Malignant-functioning neuroendocrine tumors of the pancreas: a survival analysis. Surgery 2016;159:1382—9.
[9] Keutgen XM, Nilubol N, Glanville J, Sadowski SM, Liewehr DJ, Venzon DJ, et al. Resection of primary tumor site is associated with prolonged survival in metastatic nonfunctioning pancreatic neuroendocrine tumors. Surgery 2016;159:311—8.
[10] Gloppel G. Neuroendocrine neoplasms: dichotomy, origin and classifications. Visceral Med 2017;33:324—30.
[11] Teo R, Goh BKP, Tai DWM, Allen JC, Lim TKH, Hwang JSG, et al. Validation and comparison between current prognostication systems for pancreatic neuroendocrine neoplasms: a single-institution experience with 176 patients. Surgery 2017;161:1235—45.
[12] Boninsegna L, Panzuto F, Partelli S, Capelli P, Delle Fave G, Bettini R, et al. Malignant pancreatic neuroendocrine tumour: lymph node ratio and Ki67 are predictors of recurrence after curative resections. Eur J Cancer 2012;48:1608—15.
[13] Cherenfant J, Talamonti MS, Hall CR, Thurow TA, Gage MK, Stocker SJ, et al. Comparison of tumor markers for predicting outcomes after resection of nonfunctioning pancreatic neuroendocrine tumors. Surgery 2014;156:1504—10.
[14] Sallinen V, Haglund C, Seppänen H. Outcomes of resected nonfunctional pancreatic neuroendocrine tumors: do size and symptoms matter? Surgery 2015;158:1556—63.
[15] Ricci C, Casadei R, Taffurelli G, Campana D, Ambrosini V, Pagano N, et al. Validation of the 2010 WHO classification and a new prognostic proposal: a single centre retrospective study of well-differentiated pancreatic neuroendocrine tumours. Pancreatology 2016;16:403—10.
[16] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence — SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2015 Sub (1973—2013 varying) — Linked To County Attributes — Total US, 1969—2014 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2016, based on the November 2015 submission.
[17] Collett D. Modelling survival data in medical research. London: Chapman and Hall; 1994.
[18] McCullagh P, Nelder JA. Generalized linear models, chapter 2. 2nd ed. London: Chapman and Hall; 1989.
[19] Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515—26.
[20] Preston DL. Poisson regression in epidemiology. In: Armitage P, Colton T, editors. Encyclopedia of biostatistics. John Wiley & Sons, Ltd.; 2005. [Published online July 15, 2005. Available at http://onlinelibrary.wiley.com/doi/10.1002/0470011815.b2a03094/full. DOI: 10.1002/0470011815.b2a03094].
[21] Human Mortality Database. University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). [Available at www.mortality.org or www.humanmortality.de (data downloaded on January 15, 2018)].
[22] Arias E. United States life tables, 2010. National vital statistics reports; vol. 63 No. 7. Hyattsville, Maryland: National Center for Health Statistics; 2014.

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