Clinical presentation, recurrence, and survival in patients with neuroendocrine tumors: results from a prospective institutional database

Monica Ter-Minassian[1,2], Jennifer A Chan[1], Susanne M Hooshmand[1], Lauren K Brais[1], Anastassia Daskalova[1], Rachel Heafield[1], Laurie Buchanan[1], Zhi Rong Qian[1], Charles S Fuchs[1], Xihong Lin[3], David C Christiani[2] and Matthew H Kulke[1]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Dana 1250, 450 Brookline Avenue, Boston, Massachusetts 02215, USA
Departments of [2]Environmental Health [3]Biostatistics, Harvard School of Public Health, Boston, Massachusetts 02115, USA

Correspondence should be addressed to M Ter-Minassian
Email
monica_ter-minassian1@dfci.harvard.edu

Abstract

The rarity of neuroendocrine tumors (NET) has contributed to a paucity of large epidemiologic studies of patients with this condition. We characterized presenting symptoms and clinical outcomes in a prospective database of over 900 patients with NET. We used data from patient questionnaires and the medical record to characterize presenting symptoms, disease-free survival (DFS), and overall survival (OS). The majority of patients in this database had gastroenteropancreatic NET. The median duration of patient-reported symptoms before diagnosis was 3.4 months; 19.5% reported durations from 1 to 5 years, 2.5% from 5 to 10 years, and 2% >10 years. The median DFS among patients with resected small bowel NET or pancreatic NET (panNET) was 5.8 and 4.1 years respectively. After correcting for left truncation bias, the median OS was 7.9 years for advanced small bowel NET and 3.9 years for advanced panNET. Chromogranin A (CGA) above twice the upper limit of normal was associated with shorter survival times (hazard ratios 2.8 (1.9, 4.0) $P<0.001$) in patients with metastatic disease, regardless of tumor subtype. Our data suggest that while most NET patients are diagnosed soon after symptom onset, prolonged symptom duration before diagnosis is a prominent feature of this disease. Though limited to observations from a large referral center, our observations confirm the prognostic value of CGA and suggest that median survival durations may be shorter than that reported in other institutional databases.

Key Words
- neuroendocrine tumors
- disease-free survival
- overall survival
- chromogranin A

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Introduction

A low incidence of neuroendocrine tumors (NET) has presented challenges to completing large epidemiologic studies characterizing the clinical presentation and course of patients with this condition (Yao *et al.* 2008). Data on the type and duration of symptoms before the diagnosis of NET may lead to earlier diagnosis (Modlin *et al.* 2008). Additionally, a clearer understanding of the natural history and prognostic factors for patients with NET may facilitate the development of treatment guidelines and the design of clinical trials (Modlin *et al.* 2008, Kulke *et al.* 2011).

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While symptoms of hormone hypersecretion are a hallmark of NET, only a minority of patients have been reported to exhibit such symptoms at the time of their initial presentation (Pape *et al.* 2008*a*,*b*, Yao *et al.* 2008, Zerbi *et al.* 2010, Jann *et al.* 2011). Presenting signs and symptoms for patients with symptoms of hormone hypersecretion are thought to occur, on average, for many years before diagnosis (Vinik *et al.* 2009, 2010). Few studies, however, have evaluated the time to presenting signs and symptoms of NET patients.

Clinical outcomes of patients with NET have been assessed in population-based cohorts and in institutional databases, but data on disease-free survival (DFS) estimates in these studies are limited (Pape *et al.* 2008*a*,*b*, Yao *et al.* 2008, Zerbi *et al.* 2010, Jann *et al.* 2011). Additionally, survival estimates for patients with advanced disease are highly variable. In an analysis of over 35 000 NET cases in the SEER database, the median survival duration was 2 years for patients with metastatic pancreatic NET (panNET) and 4.7 years for patients with metastatic small bowel NET tumors (Yao *et al.* 2008). Institutional studies, on the other hand, have reported median survival durations of 5.8–7.4 years for patients with advanced panNET (Pape *et al.* 2008*a*, Strosberg *et al.* 2008, 2011) and over 10 years for patients with metastatic small bowel NET (Pape *et al.* 2008*a*, Jann *et al.* 2011).

Tumor stage, tumor grade, and site of tumor origin are well-established prognostic factors for patients with NETs (Solcia *et al.* 2000, Rindi *et al.* 2006, Pape *et al.* 2008*b*, Strosberg *et al.* 2011). However, the role of biochemical markers such as chromogranin A (CGA) or alkaline phosphatase (ALP) in assessing prognosis remains controversial. While several studies have reported associations between elevated CGA increased disease burden and shorter survival (Janson *et al.* 1997, Stivanello *et al.* 2001, Kolby *et al.* 2004, Nehar *et al.* 2004, Ekeblad *et al.* 2008, Nikou *et al.* 2008, Korse *et al.* 2009, Yao *et al.* 2011, 2012), CGA can be elevated in non-malignant conditions and associations with high prognosis have not been uniformly observed (Lawrence *et al.* 2011*a*). Elevated ALP has been reported to be associated with shorter survival in patients with advanced NET by our group and by others (Clancy *et al.* 2006, Kwekkeboom *et al.* 2011).

To better define and compare the clinical presentation and subsequent course of patients with small bowel, pancreatic, and other NETs, we used data from a prospectively collected institutional database, based in a gastrointestinal oncology unit, comprising over 900 patients with NET. We evaluated patient-reported presenting symptoms, disease-free, and overall survival (OS), together with potential prognostic factors.

Materials and methods

Assessment of presenting symptoms, baseline demographics, and clinical outcomes

Patients with a confirmed diagnosis of NET (excluding small cell lung cancer) were recruited to an IRB-approved study in the gastrointestinal clinic at Dana-Farber Cancer Institute (DFCI) beginning in July 2003. Consent had been obtained from each patient after a full explanation of the purpose and nature of all procedures used. Data on presenting signs and symptoms were obtained from patient questionnaires. Baseline clinical and demographic information was derived from both questionnaires and from the medical record. All pathology was reviewed in the Pathology Department at Dana-Farber/Brigham and Women's Cancer Center at the time of patient consultation (2003–2010). For the purposes of this project, each case was assigned a tumor grade (low, intermediate, or high) best corresponding to the World Health Organization (WHO) 2010 classification: G1, G2, and G3 (Klimstra *et al.* 2010, Rindi *et al.* 2010). Assignments were based on available information in the pathology report on tumor grade, tumor differentiation, mitotic rate, and the Ki-67 labeling index; tissue blocks were not re-reviewed due to inconsistent availability. Serum ALP and serum CGA values were extracted from clinical laboratory test reports. Testing for CGA was performed at either Quest Diagnostics or Mayo Medical Research clinical labs.

Variables associated with symptom duration before diagnosis were evaluated by a multivariate Cox proportional hazards regression analysis, adjusting for age and stage at diagnosis, gender, tumor origin, and tumor grade.

Assessment of DFS and OS

Patients were categorized as having either small bowel NET, panNET or other NET. Survival data were obtained from the medical record, or, if not available, from the Social Security Death Index. In patients without distant metastases at the time of diagnosis, DFS was calculated from the date of primary tumor resection to the date of the first outcome in the following order: local recurrence, development of distant metastases, death from any cause, or to the censoring date (the date of the patient's last visit at the DFCI). OS was calculated from the date of diagnosis of metastatic disease to the date of death or to the date of

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censoring (October 21, 2010). Median times for DFS and OS were estimated using the Kaplan–Meier method, comparisons were assessed by the log-rank test. Left truncation bias can lead to overestimates of standard survival distributions caused by the variable times between initial or metastatic diagnosis and entry into the study at consent date. To account for this, OS was also estimated using a modified Kaplan–Meier method using SAS macro *survlt*; http://mayoresearch.mayo.edu/mayo/research/biostat/sasmacros.cfm (Shariff *et al*. 2008, Cain *et al*. 2011, Strosberg *et al*. 2011). Median follow-up time was computed among censored observations only, adjusting for left truncation using the baseline survival curve of a Cox proportional hazards model with no covariates, accounting for entry time by consent date.

Assessment of prognostic factors

We assessed potential prognostic factors using patients with complete information on age, gender, tumor stage (metastatic or localized at initial diagnosis), tumor subtype (small bowel NET, panNET, other NET), and tumor grade (low, intermediate, high, and unknown). We used a multivariate Cox proportional hazards regression analyses accounting for left truncation with entry at the consent date. For analysis of serum CGA and ALP, we included patients with an available measurement closest to the time of metastatic diagnosis. CGA and ALP were categorized as binary categorical variables (elevated/non-elevated above the upper limit of normal). All statistical testing was done at the two-sided 0.05 alpha level, using SAS software version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Nine hundred thirty-seven patients were enrolled in the prospective database between July 2003 and October 2010 (Table 1). Consent rates for the study exceeded 95%. Dates of initial diagnosis ranged from June 1958 to February 2010. The median patient age was 54 years; 411 patients (44%) had localized disease and 526 (56%) had distant metastases at the time of their initial diagnosis. Of those with localized disease, all but 24 underwent surgical resection. In light of the diversity of NET, we focused our subsequent analyses on the two most common subgroups: small bowel NET and panNET which comprised 38 and 23% of the cohort respectively. Other NET represented 39% of the cohort and comprised a diverse group of NET arising in other sites, including NETs of unknown primary site (11%), bronchi (9%), appendix (5%), stomach (3%), and of other origins (11%). Nearly, all (97%) small bowel NET tumors were well differentiated; 86% of panNET and 78% of other NET had well differentiated histology.

Table 1 Baseline characteristics of the patient population.

	All patients ($n=937$)[a]	**Small bowel NET** ($n=358$)	**Pancreatic NET** ($n=215$)	**Other NET** ($n=364$)
Median age at diagnosis (years) (range)	54 (13.2–86.4)	57 (26.6–86.4)	53 (13–85.8)	51 (14.3–86.2)
Gender (M, F)	435 (46.4%), 502 (53.6%)	178 (50%), 180 (50%)	109 (50.7%), 106 (49.3%)	148 (40.7%), 216 (59.3%)
Ethnicity (Caucasian, African-American, Other)	878 (93%), 24 (3%), 35 (4%)	337 (94%), 12 (3%), 9 (3%)	204 (95%), 2 (1%), 9 (4%)	337 (93%), 10 (2%), 17 (6%)
Tumor grade				
Low	815 (86.97%)	347 (96.9%)	184 (85.6%)	284 (78%)
Intermediate	56 (5.98%)	6 (1.7%)	16 (7.4%)	34 (9.3%)
High	34 (3.63%)	1 (0.3%)	11 (5.12%)	22 (6%)
Unknown	32 (3.42%)	4 (1.1%)	4 (1.9%)	24 (6.6%)
Stage				
Localized at diagnosis	411	129	77	205
LN[b]+	172 (49%)	98 (82.3%)	31 (51%)	43 (25%)
LN[b]−	182 (51%)	21 (17.6%)	30 (49%)	131 (75%)
Unknown	57	10	16	31
Metastatic[c]	677	272	182	223
At diagnosis	526	229	138	159
After F/U	151	43	44	64

[a]Total cases include small bowel NET (38%), pancreatic NET (23%) and other NET (unknown primary site (11%), bronchi (9%), appendix (5%), stomach (3%), and of other origins (11%)).
[b]Resected patients with lymph node status.
[c]Patients with distant metastases at diagnosis or during follow-up.

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Symptoms at initial presentation

Seven hundred thirty-one (78.0%) patients completed questionnaires, characterizing symptoms leading to their diagnosis. Abdominal discomfort was the most common presenting symptom for patients with gastrointestinal tumor (Fig. 1A). Twenty-four percent of the patients were diagnosed either during screening procedures or procedures performed for other reasons (20% for panNET, 20% for small bowel NET, 30% for other NET). Among patients with small bowel NET, 12% presented with symptoms of diarrhea and 7% reported symptoms of flushing.

The reported presenting symptoms differed to some extent between patients with localized or metastatic disease (Fig. 1B and C). While abdominal pain was a common presenting symptom in both subsets, incidental diagnosis was more common among patients with localized disease than in those whose disease was metastatic (33 vs 17%). In contrast, symptoms of flushing or diarrhea were less common in patients with localized disease than in those with metastases at diagnosis. Flushing was reported in 2% of patients with localized disease vs 6% metastatic. Diarrhea was reported in 6% of patients with localized disease vs 13% metastatic.

To estimate the time from onset of symptoms to diagnosis, we limited our analysis to the 393 patients who reported a date of initial symptoms before diagnosis and excluded patients who reported no symptoms or who were incidentally diagnosed. Median time from onset of symptoms to diagnosis was 3.4 months for the cohort overall, and 4.3, 2.9, and 2.9 months for patients with small bowel NET, panNET, and other NET respectively (Fig. 1D).

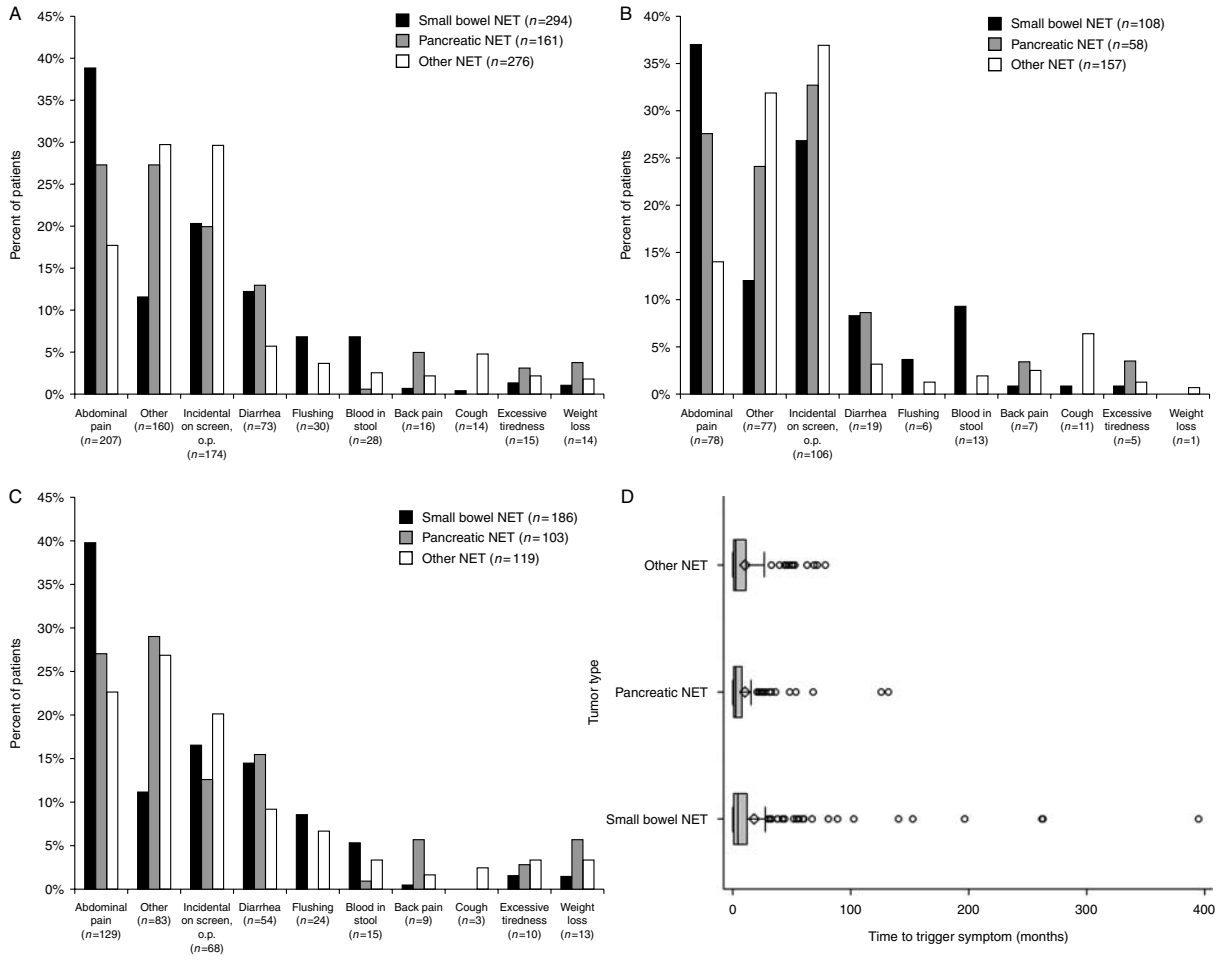

Figure 1

(A, B and C) Patient-reported symptoms at time of diagnosis. (A) Patient-reported symptoms, entire cohort ($n=731$). (B) Symptoms reported by patients presenting with localized disease ($n=323$). (C) Symptoms reported by patients with metastatic disease ($n=408$). (D). Patient-reported time from initial onset of symptoms to diagnosis ($n=393$).

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However, some patients reported prolonged symptom duration before diagnosis; in the cohort overall, 19.5% reported durations from 1 to 5 years, 2.5% from 5 to 10 years, and 2% >10 years. A multivariate regression model showed that only high tumor grade was significantly associated with a shorter time from the onset of symptoms to diagnosis aHR 2.5 (1.6, 4.0), $P<0.001$.

To address the possible effect of recall bias, we also evaluated presenting symptoms in the 213 patients who consented to the study within 6 months of their diagnosis. While the calculated time durations were slightly shorter that for the cohort overall, we found a similar pattern in that the median time from initial symptoms to diagnosis was relatively short (2.7 months) while 14.5% reported durations from 1 to 5 years, 1.9% from 5 to 10 years, and 1.4% >10 years.

Disease-free survival

Four hundred eleven patients without distant metastases underwent resection of their primary tumor; of these, 354 had known lymph node status and were used to estimate DFS. Of these 354 patients, 124 of these patients experienced a recurrence: 102 before study enrollment, and 22 after study enrollment. Five year DFS rates were 56% in the cohort overall; 57% in small bowel NET, and 42% in panNET. The median DFS was 5.8 years in the cohort overall, 5.8 years for patients with small bowel NET and 4.1 years for those with panNET (Table 2 and Fig. 2A).

Lymph node involvement was associated with shorter DFS in the cohort overall (Table 3) and in patients with small bowel NET but not in panNET (Table 2). Patients with small bowel NET also had a higher incidence of positive lymph nodes (82%) than other subgroups. Among patients with resected small bowel NET and no lymph node involvement, only 2 of 21 experienced a recurrence, and the median DFS was not reached. Among patients with resected small bowel NET and lymph node involvement, 37 of 98 experienced a recurrence; these patients had a median DFS of 5.6 years (Table 4).

Overall survival

There were 270 deaths during the course of the study, the median follow-up time was 4.2 years and the mean follow up time was 6 years (range of 6.4 months to 52.4 years). Due to a low number of deaths in resected patients, we were not able to accurately estimate OS for this cohort, so we limited our survival estimates to patients with unresectable, metastatic disease. Our initial estimated median OS duration for metastatic patients was 8.0 years for the cohort overall, 10.1 years for small bowel NET, 5.9 years for panNET, and 5.9 years for other NET. Previous studies have noted that 'immortal time bias' or 'left truncation bias' may artificially inflate survival estimates due to the inclusion of patients who have been diagnosed many years before evaluation at a referring institution, and therefore have longer than average survival (Shariff

Table 2 Disease-free and overall survival duration.

	Overall cohort		Small bowel NET		Pancreatic NET		Other NET	
	Events/*n*	Median survival time (years)	Events/*n*	Median survival time (years)	Events/*n*	Median survival time (years)	Events/*n*	Median survival time (years)
Disease free survival (patients with resected, localized disease[a])								
All patients[a]	124/354	5.8	39/119	5.8	34/61	4.1	51/147	7.3
LN− LN+, Log-rank *P*	48/182, 76/172	7.7, 5.0, $P=0.001$	2/21, 37/98	Not reached, 5.6, $P=0.05$	15/30, 19/31	4.6, 4.0, $P=0.7$	31/131, 20/43	7.8, 5.0, $P=0.002$
Overall survival (patients with distant metastases[b])								
Uncorrected	267/677	8.0	77/272	10.1	87/182	5.9	103/223	5.9
Diagnosed within 1 year of consent	125/357	6.0	34/151	7.9	43/94	4.7	48/112	4.5
Corrected for left truncation bias	267/677	5.2	77/272	7.9	87/182	3.9	103/223	3.7

[a]Limited to those with documented lymph node (LN) status.
[b]Metastases at initial presentation or during follow-up.

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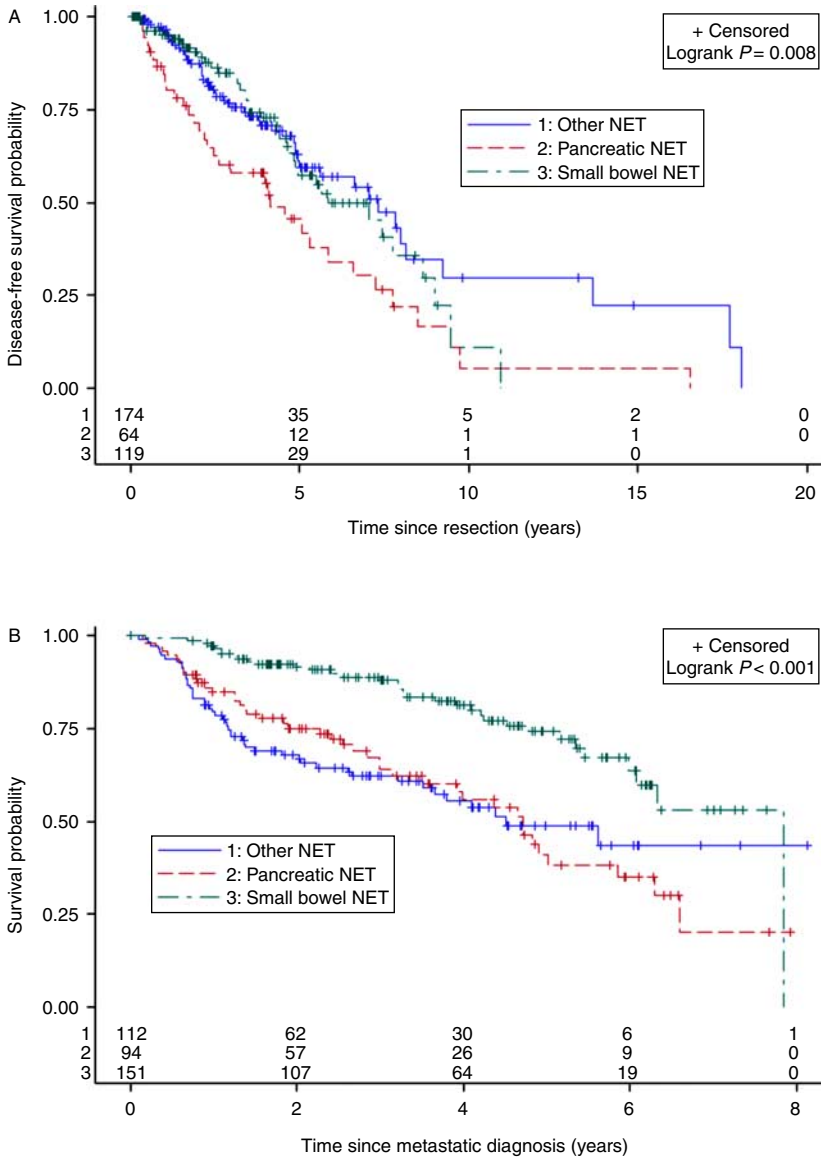

Figure 2

(A) Disease-free survival following resection according to tumor site of origin. (B) Overall survival for patients with metastatic disease according to tumor subtype (analysis limited to patients diagnosed within 1 year of study). Full colour version of this figure available via http://dx.doi.org/10.1530/ERC-12-0340.

et al. 2008, Strosberg *et al*. 2011). Using a modified Kaplan–Meier analysis that corrects for left truncation bias, we estimated the median survival duration to be 5.2 years for the cohort overall, 7.9 years for small bowel NET, 3.9 years for panNET, and 3.7 years for other NET (Table 2). We obtained similar results when we restricted our analysis to patients diagnosed within 1 year (Fig. 2B), another approach that would mitigate left truncation bias. Intermediate or high tumor grade, older age, and pancreatic primary site were independent adverse prognostic factors in patients with advanced NET (Table 4).

We assessed associations between the biomarkers CGA or ALP and survival from the date each test was obtained. We used any available test results closest to the date of diagnosis of metastatic disease that was within 2–3 months on average, with a range of 0–14 years for both markers. CGA above the upper limit of normal was associated with shorter survival in patients with metastatic small bowel NET or non-panNET; however using this cutoff we did not observe a statistically significant association between elevated CGA and survival in panNET. Using a CGA cutoff of twice the upper limit of

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Table 3 Prognostic factors for disease-free survival (resected patients; $n=354$).

Variable	Adjusted HR[a] (95% CI)
Older age	1.0 (0.9, 1.0), $P=0.07$
Male gender	1.2 (0.9, 1.8), $P=0.3$
Lymph node involvement	1.9 (1.3, 3.0), $P=0.003$
Tumor grade	
Intermediate	3.1 (1.8, 5.3), $P<0.001$
High	5.5 (1.6, 18.2), $P=0.006$
Unknown	1.4 (0.3, 6.0), $P=0.6$
Primary site	
panNET vs other	1.5 (0.9, 2.3), $P=0.1$
SBN vs other	0.9 (0.5, 1.5), $P=0.6$
panNET vs SBN	1.7 (1.0, 2.8), $P=0.04$

panNET, pancreatic NET; SBN, small bowel NET; Other, other NET.
[a]Hazard ratios adjusted for age at diagnosis, gender, indicator variables of tumor type, tumor grade and lymph node status.

normal, we observed an association between elevated levels and shorter survival in the cohort overall (adjusted HR 2.8 (1.9, 4.0), $P<0.001$) (Table 5) and significant associations in all subgroups. ALP levels above the normal upper limit were associated with shorter survival in the cohort overall (Table 5) and in both the small bowel NET and non-panNET subgroups. We did not observe a significant association between elevated ALP and survival for patients with advanced panNET.

Discussion

Our study provides detailed data on presenting symptoms and clinical outcomes in a large, highly annotated institutional cohort of NET patients. The majority of patients in our cohort had gastroenteropancreatic NET; we focused our analyses on two major subgroups: small bowel NET and panNET. We found that delays in diagnosis from initial symptoms were shorter than previously reported. We also noted that median disease-free and OS times were shorter than other institutional studies, but OS was longer than population-based estimates. Elevated serum biomarkers CGA and ALP were prognostic factors for OS in patients with metastatic disease.

The distribution of tumor subgroups in our cases differs from population estimates (Maggard *et al*. 2004, Yao *et al*. 2008) and reflects a higher proportion of small bowel and panNETs, likely due to accrual centered at a gastrointestinal cancer clinic. In a recently published large NET study, Faggiano *et al*. (2012) describe the characteristics of 820 NET from a multicenter Italian cohort, where the percentage of lung NETs was higher (29% vs our 8%). When restricted to gastrointestinal NETs alone, the relative frequencies in our cohort are similar to those reported in population-based series (Maggard *et al*. 2004).

Abdominal pain was the most common presenting symptom in our cohort. However, a high proportion (24% in our study) was diagnosed incidentally, consistent with prior reports (Pape *et al*. 2008*a*, Zerbi *et al*. 2010, Strosberg *et al*. 2011, Faggiano *et al*. 2012). Our observations similarly confirm previous studies that initial presentation with symptoms of hormone hypersecretion is relatively uncommon (14% in our cohort), and when it does occur patients are more likely to already have metastatic disease (Boudreaux *et al*. 2010, Kulke *et al*. 2010, Jann *et al*. 2011, Faggiano *et al*. 2012).

Published reports have also suggested that delays in diagnosis are common in patients with NETs (Modlin *et al*. 2008, Vinik *et al*. 2010). Using patient-reported surveys, we found that, encouragingly, the majority of patients was diagnosed <4 months after symptom onset. We also noted, however, that 19.5% of patients were diagnosed from 1 to 5 years after symptom onset, suggesting that prolonged symptom duration before diagnosis remains a prominent feature of this disease.

Reports on DFS durations for patients with resected NETs are relatively scarce (Pape *et al*. 2008*a*, Casadei *et al*. 2010, Kimura *et al*. 2011, Landerholm *et al*. 2011, Boninsegna *et al*. 2012, Strosberg *et al*. 2012). Previous studies have reported median DFS durations of 88 months following resection of ileal NET (Landerholm *et al*. 2011, Le Roux *et al*. 2011) and 80–85 months following resection of panNET (Gomez-Rivera *et al*. 2007, Boninsegna *et al*. 2012). Our median DFS estimates of 70.1 months for patients with small bowel NET and 49.5 months for patients with panNET are somewhat shorter than these previous estimates. Differences in stage distributions did

Table 4 Prognostic factors for overall survival (metastatic patients; $n=677$).

Variable	Adjusted HR[a] (95% CI)
Older age	1.02 (1.01, 1.03), $P<0.001$
Male gender	1.2 (0.9, 1.5), $P=0.3$
Stage at diagnosis	1.4 (1.0, 1.9), $P=0.05$
Tumor grade	
Intermediate	1.6 (1.04, 2.5), $P=0.03$
High	3.9 (2.5, 6.0), $P<0.001$
Unknown	1.5 (0.8, 2.8), $P=0.2$
Primary site	
panNET vs Other	1.0 (0.8, 1.4), $P=0.8$
SBN vs Other	0.5 (0.3, 0.6), $P<0.001$
panNET vs SBN	2.3 (1.7, 3.2), $P<0.001$

panNET, pancreatic NET; SBN, small bowel NET; Other, other NET.
[a]Hazard ratios adjusted for age at diagnosis, gender, indicator variables of tumor type, tumor grade; corrected for left truncation.

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Table 5 Prognostic value of chromogranin A or alkaline phosphatase in advanced NET.

	Overall cohort		Small bowel NET		Pancreatic NET		Other NET	
	aHR (95%CI)[a]	Events/*n*	aHR (95%CI)	Events/*n*	aHR (95%CI)	Events/*n*	aHR (95%CI)	Events/*n*
Chromogranin A								
WNL	Ref	29/107	Ref	10/56	Ref	9/17	Ref	10/34
>1xUNL	2.2 (1.5, 3.4), $P<0.001$	117/242	2.2 (1.1, 4.4), $P=0.03$	242/112	1.5 (0.7, 3.3), $P=0.4$	38/65	2.9 (1.4, 6.2), $P=0.005$	37/65
WNL	Ref	43/160	Ref	13/83	Ref	16/35	Ref	14/42
>2xUNL	2.8 (1.9, 4.0), $P<0.001$	103/189	3.5 (1.9, 6.8), $P<0.001$	39/85	2.7 (1.4, 5.2), $P=0.004$	31/47	2.4 (1.2, 4.7), $P=0.01$	33/57
Alkaline phosphatase								
WNL	Ref	88/244	Ref	36/131	Ref	25/43	Ref	27/70
>1xUNL	2.0 (1.4, 2.8), $P<0.001$	65/106	2.4 (1.3, 4.4), $P=0.005$	16/32	1.1 (0.6, 2.0) $P=0.8$	26/45	3.7 (1.9, 6.7), $P<0.001$	23/29

UNL, upper limit of normal; WNL, within normal limit.
[a]Adjusted hazard ratios (aHR) calculated from time of test, adjusted for age at diagnosis, gender, indicator variables of tumor type, tumor grade, and elevated chromogranin A or elevated alkaline phosphatase.

not seem to explain the shorter DFS observed in our cohort; our observed 5-year DFS for panNET with positive lymph nodes was 39% which is lower than the 53% reported for ENETS stage III patients (Strosberg *et al.* 2012). We note that the majority of resected patients developed a recurrence before study enrollment; it seems likely that selective referral of patients who developed earlier recurrence may has influenced our estimates and resulted in shorter DFS estimates than in other studies.

Pathology classification systems for NETs have evolved over time, and rereview of all tumor blocks was not feasible in our dataset. However, we observed that, as in prior studies (Casadei *et al.* 2010, Kimura *et al.* 2011), intermediate and high tumor grades were associated with shorter DFS across tumor subtypes. Additionally, lymph node involvement was associated with shorter DFS in patients with resected small bowel or non-panNET, as previously reported (Le Roux *et al.* 2011). We did not observe a strong association between lymph node involvement and shorter DFS in patients with panNET. Others have also failed to identify associations between lymph node involvement and DFS in panNET, and have suggested that lymph node ratio, rather than presence or absence of lymph nodes, may be a better prognostic measure for such patients (Gomez-Rivera *et al.* 2007, Casadei *et al.* 2010, Boninsegna *et al.* 2012).

Published estimates of median survival times for patients with metastatic NETs are variable. Population-based studies have generally reported shorter times than studies based on institutional cohorts (Yao *et al.* 2008). A multiplicity of diagnosis codes for NETs, as well as a requirement for a 'malignant' diagnosis, may have affected the inclusion of patients in the population-based SEER database and influenced survival estimates in SEER-based studies (Modlin *et al.* 2008, Yao *et al.* 2008, Lawrence *et al.* 2011*b*). At the same time, selection bias likely overestimates published survival estimates based on data from tertiary referral centers (Pape *et al.* 2008*a*,*b*, Strosberg *et al.* 2008, Jann *et al.* 2011). 'Immortal time bias' or 'left truncation bias' in institutional databases, resulting from the selective inclusion of patients with a favorable prognosis who were diagnosed years before evaluation, has been reported to be an important factor in epidemiologic studies of survival, including studies of NETs (Shariff *et al.* 2008, Strosberg *et al.* 2011). When we accounted for this bias using a modified Kaplan–Meier analysis and Cox regression, we estimated an overall median survival duration of 5.2 years for patients with metastatic NETs. As in prior studies, we observed differences in OS depending on site of tumor origin, with patients who had metastatic small bowel NET tumors experiencing longer survival durations (7.9 years) than those with panNET (3.9 years). These values fall midway between SEER estimates (4.7 and 2 years respectively (Yao *et al.* 2008)) and uncorrected estimates from other large institutional series (10 and 5.8–7.5 years respectively), and may represent a more realistic estimate for survival in this patient population. These estimates compare favorably to those for advanced colorectal or pancreatic adenocarcinoma, where 5-year survival rates are estimated to be only 12 and 1.8% respectively (Howlader *et al.* 2009) http://seer.cancer.gov/csr/1975_2009_pops09/(accessed 2012).

Associations between elevated CgA and shorter survival have also been reported in small bowel NET and panNET (Janson *et al.* 1997, Arnold *et al.* 2008, Ekeblad *et al.* 2008, Nikou *et al.* 2008, Korse *et al.* 2009, Yao *et al.* 2011). Unanticipated imbalances in CGA between the two arms of a recent randomized trial of patients with advanced NET

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have been reported to have adversely affected trial outcome (Yao *et al*. 2012). Our observations confirm that when a cutoff of twice the upper limit of normal is used, elevated CGA is strongly associated with shorter survival in patients with advanced NET (Howlader *et al*. 2009). We additionally observed an association between elevated ALP and shorter survival in metastatic patients overall, although the hazard ratio was lower than that observed with CGA. We did not observe a statistically significant association between ALP levels and survival in the subgroup of patients with advanced panNET, although this finding may in part be related to the smaller sample size of this subgroup.

In summary, our data, though limited to a single large referral center and subject to potential referral bias, suggest that disease-free and OS times for patients with NET, while longer than those for patients with other malignancies, may be shorter than those reported in other institutional databases. We observed a high rate of incidental diagnosis, and in a subgroup of NET patients, prolonged times from symptom onset to diagnosis, suggesting that further effort is needed to facilitate an early diagnosis in patients with NET. For patients with advanced disease, CGA is a robust prognostic marker. The time estimates and prognostic factors identified in this large analysis may be useful in facilitating both the clinical care and the design of trials of therapeutic agents in this disease.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. M H Kulke has served as a consultant to Pfizer, Novartis, and Ipsen. C S Fuchs has served as a consultant to Amgen, Sanofi-Aventis, Pfizer, Genentech, Roche, and Bayer.

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