Surgery 165 (2019) 760–766

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Prognostic significance of Chromogranin A in small pancreatic neuroendocrine tumors ☆

Mustafa Raoof, MD[a], Zeljka Jutric, MD[b], Laleh G. Melstrom, MD[a], Byrne Lee, MD[a], Daneng Li, MD[c], Susanne G. Warner, MD[a], Yuman Fong, MD[a], Gagandeep Singh, MD[a,*]

[a] Department of Surgery, City of Hope National Medical Center, Duarte, CA
[b] Department of Surgery, University of California, Irvine, CA
[c] Department of Medical Oncology, City of Hope National Medical Center, Duarte, CA

ARTICLE INFO

Article history:
Accepted 15 October 2018
Available online 15 November 2018

ABSTRACT

Background: The incidence of nonfunctional pancreatic neuroendocrine tumors ≤2cm is rising. The biologic behavior of these tumors is variable; thus, their management remains controversial. Chromogranin A upregulation is a useful diagnostic biomarker of neuroendocrine tumors; however, the prognostic significance of Chromogranin A is unclear. The objective of this study was to determine whether Chromogranin A levels have prognostic value in pancreatic neuroendocrine tumor patients and may help guide management.

Methods: We evaluated the National Cancer Database over a 10-year period (2004–2013). Patients with pancreatic neuroendocrine tumors measuring ≤2cm, without distant metastases, were identified and categorized as Chromogranin A high (>420ng/mL) or Chromogranin A low (≤420ng/mL), and those lacking data on Chromogranin A levels were excluded from the study. Univariate and multivariate analyses were performed using Cox proportional hazards model. Cut-point determination was performed using the Contal and O'Quigley method.

Results: Of the 445 eligible patients, 352 (79%) were Chromogranin A low and 93 (21%) were Chromogranin A high. Median Chromogranin A level was 71ng/mL (interquartile range, 24–294ng/mL). Chromogranin levels were associated with clinical nodal status and grade. Furthermore, on multivariate analysis, Chromogranin A levels (Chromogranin A high versus Chromogranin A low) independently predicted overall survival after controlling for tumor size, grade, clinical nodal status, and academic status of the facility (hazard ratio: 7.90, 95%CI: 2.34–26.69, $P = .001$). The greatest benefit of surgical resection was noted in patients in the Chromogranin A high subgroup (log-rank $P < .001$).

Conclusion: Serum Chromogranin A levels can be incorporated in surgical decision-making for patients with small pancreatic neuroendocrine tumors. Patients in the Chromogranin A low group can be considered for observation, whereas patients in the Chromogranin A high group should be strongly considered for resection.

Introduction

Pancreatic neuroendocrine tumors (PNETs) are rare tumors that originate in the pancreas with a more favorable prognosis than pancreatic ductal adenocarcinoma.[1,2] Because of the rarity of these tumors, the management is guided by observational data from retrospective studies. Over the past 2 decades the incidence of nonfunctioning PNETs (NF-PNETs) has increased.[1–3] This is largely attributable to the improved quality and increased use of cross-sectional imaging.

Tumor size, grade (mitotic count and Ki-67), and nodal status are the main prognostic determinants of nonmetastatic PNETs.[3–5] Current guidelines recommend surgical resection for PNETs that are greater than 2 cm in size.[6,7] For those that are 2 cm or smaller, significant controversy exists as the behavior of these tumors is uncertain. Studies analyzing the natural history of small PNETs demonstrate a median growth rate of about a 0.12 mm per year.[8] Because the majority of these tumors are low grade and have a relatively benign course, many studies support observation for

☆ Presented at the American Society of Clinical Oncology GI Symposium, January 19–21, 2017 and at the Society of Surgical Oncology, March 15–18, 2017.

* Corresponding author: Chief, Division of Surgical Oncology Head, Hepatobiliary an Pancreatic Surgery, Department of Surgery, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, California, 91016.
E-mail address: gsingh@coh.org (G. Singh).

https://doi.org/10.1016/j.surg.2018.10.018
0039-6060/

small PNETs.[9–12] This is reflected in the guidelines put forth by the European Neuroendocrine Tumor Society that state that intensive observation could be considered for NF-PNETs <2 cm, but risks and benefits must be carefully weighed in each patient.[6] However, some recent studies have suggested that upfront surgical resection regardless of tumor grade confers a survival advantage.[13–15] It is possible that within this subset of small PNETs there are those with more aggressive behavior not characterized by current prognostic determinants.

Chromogranin A (CgA) is a hydrophilic glycoprotein that undergoes proteolysis and is converted to bioactive peptides upon release by postganglionic sympathetic neurons and adrenal chromaffin cells.[16] Its usefulness in the diagnosis of all neuroendocrine tumors has been very well characterized, with elevation noted on 70% of all PNETs.[17–19] CgA levels correlate with tumor burden in metastatic disease, but prognostic significance in localized disease is uncertain.[20,21]

We hypothesized that preoperative CgA levels are prognostic in small (<2 cm) PNETs. This study tested this hypothesis using a large clinical oncology database and also determined the optimal cutoff to be used for decision-making with regards to upfront surgical resection or watchful waiting.

Methods

The National Cancer Database (NCDB), jointly sponsored by the Commission on Cancer of the American College of Surgeons and the American Cancer Society, is a nationwide oncology outcomes database built on more than 1,400 Commission on Cancer–accredited cancer programs, covering approximately 70% of new cancer cases in the United States.[22] This project involved publicly available, de-identified patient data and was exempt from institutional review board approval.

Patients

Patients diagnosed with NF-PNETs from 2004 to 2013 were identified based on the International Classification of Diseases for Oncology primary site codes (C250–C254, C257–C259) and histology codes (8240, 8241, 8246, 8647, and 8249). Patients were excluded if they had clinically metastatic disease at diagnosis or if they did not have data on preoperative CgA protein level available. Although the type of test or kit used to measure CgA levels was not available in the database, only results from tests that measure serum CgA levels (as opposed to plasma) are reported. Similarly, only tests that report results in standard units (ng/mL) as opposed to nonstandard units (units/L) are recorded. Patient-level variables included age, race/ethnicity, sex, Charlson-Deyo Score for comorbid conditions,[23] insurance type, tumor extent, tumor size, nodal status, and receipt of neoadjuvant or adjuvant therapies. Staging was based on the *American Joint Committee on Cancer Staging Manual, 7th edition*. The determination of grade in the NCDB is made by the pathologist and is abstracted from the final pathologic diagnosis. It was likely based on the practice guidelines during the study period and not just the morphology.[24–26] These guidelines recommend determination of morphology, mitotic counts, and Ki67. Hospital-level variables included facility type (academic: academic research program; or non-academic: community cancer program, comprehensive community cancer program, integrated cancer network program, other).

Statistical methods

Cut-point determination for optimal CgA level was performed using the minimum *P* value approach as well as Contal and O'Quigley methods described elsewhere.[27] Briefly, the data were modeled to determine whether there is an inflection point at which the CgA level shows a marked change in mortality risk, either increased or decreased, after which the new risk level remains constant. The absolute log-rank statistic was calculated using the model, which identifies the CgA level that gives the maximum difference between the subjects in the 2 groups defined by the cutoff point. A Q-statistic was calculated to test the significance of this cutoff point. The cutoff point with the highest absolute log-rank statistic and Q-statistic represents the optimal cutoff point (provided $P < .05$). Descriptive statistical analysis was performed and tabulated as medians and interquartile ranges for continuous variables, and frequencies with percentages for categorical variable. We compared patient demographics and cancer-specific and hospital-level characteristics using the Pearson chi-square test for categorical data and Kruskal-Wallis test for continuous data. Univariable and multivariable Cox proportional hazard models were used to test for associations between patient and hospital characteristics with overall survival. Forward and backward stepwise regression was used to determine the final multivariable model in survival analysis. Model selection was performed by Akaike's information criterion and Bayesian information criterion. The proportional hazards assumption was confirmed by review of Schoenfeld residuals and graphically. Hazard ratios (HR) with 95% confidence intervals (CIs) were reported. Overall survival was calculated from the date of diagnosis until the date of death and reported in months. Kaplan-Meier curves were used to depict survival differences between the 2 groups. The log-rank test was used to test these differences for statistical significance. Survivors were censored at the date of last contact, and those who died were censored at the date of death. To determine if there was institutional or assay-dependent variation in the performance of the assay, we assumed that any given hospital is likely to perform the CgA assay in-house or contract with a preferred outside lab, which is frequently the case in many hospitals across the United States. We then determined if there is evidence of clustering of CgA levels by treating hospitals after adjusting for patient- and disease-specific covariates using a mixed-effect generalized linear regression model. We limited analysis to hospitals that treated at least 10 patients to increase the likelihood that the patient cohorts among hospitals are homogenous. All analyses were performed using STATA MP Version 14 (StataCorp, College Station, TX).

Results

A total of 445 patients met inclusion criteria (Fig S1). The cohort was dichotomized into CgA high (CGH; 352, 79%) and CgA low (CGL; 93, 21%) subgroups based on a cut-point at 420ng/mL (log-rank statistic 8.84, Q-statistic 2.49, $P < .001$). The Contal and O'Quigley method of cut-point determination was used as shown in Fig. 1. The sociodemographic and clinicopathologic characteristics of CGH and CGL subgroups are presented in Table 1. Patients in the CGH group were more likely to have a higher Charlson-Deyo Score, positive nodal status (Table SI), higher grade (Table SII), and were less likely to have surgical resection and lymphadenectomy. We further explored the association of nodal status with the CGH group because pathologic nodal status was not specified for a significant number of patients. The analysis presented in Table SIII demonstrates that only about one-third of patients with missing pathologic nodal status in either group had a pancreatectomy without nodal sampling. This suggests that missing pathologic nodal status is largely and equally attributable in either group to surveillance or enucleation.

Median survival for the study participants was not reached. Median follow-up for living patients was 25 months (interquartile range: 17–32 months). Survival information was not available for the patients diagnosed in 2013 and, therefore those patients

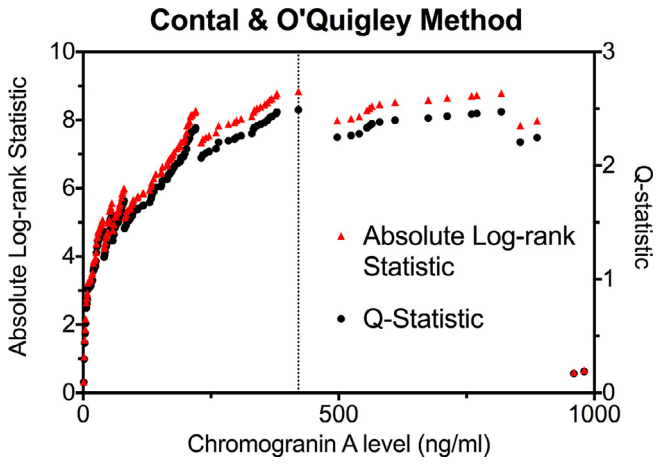

Fig. 1. Cut-point determination for Chromogranin A (CgA) level using the Contal a O'Quigley method. The data were modelled to determine whether there is an inflection point at which the CgA level shows a marked change in mortality risk, either increased or decreased, after which the new risk level remains constant. The absolute log-rank statistic was calculated using the model, which identifies the CgA level that gives the maximum difference between the subjects in the 2 groups defined by the cutoff point. A Q-statistic was calculated to test the significance of this cutoff point. The cutoff point with highest absolute log-rank statistic and Q-statistic represents the optimal cutoff point (provided $P < .05$). An optimal cut-point of 420 ng/mL was identified.

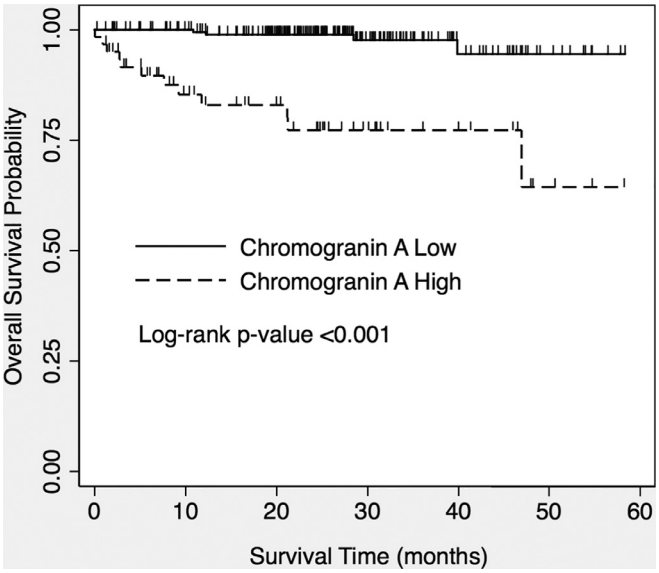

Fig. 2. Kaplan-Meier overall survival plots for patients with small (≤2 cm) pancreatic neuroendocrine tumors (PNETs) according to Chromogranin A (CgA) category. Chromogranin A low (CGL; CgA level ≤420 ng/mL) and chromogranin A high (CGH; CgA level >420 ng/mL). Equality of survival functions tested using the log-rank test.

were not included in survival analysis. Univariate and multivariate analyses of the remaining 274 patients are presented in Table 2. Factors associated with overall survival on univariate analysis include insurance, clinical nodal status, grade, surgical resection, lymphadenectomy, and CgA level, whereas age, sex, Charlson-Deyo Score, race, facility type, tumor size, and site were not associated with overall survival (Table 2).

On multivariate analysis, government insurance, positive clinical nodal status, higher grade, and CGH were independent predictors of overall survival. Kaplan-Meier overall survival estimates for CGL and CGH groups are shown in Fig. 2. There was a significant difference in the survivor functions of the 2 groups (log-rank $P < .001$; Cox proportional hazards model HR 12.54 [4.03–39.07], $P < .001$; 3-year overall survival CGL versus CGH; 98% vs. 77%). Because the majority of patients had low-grade tumors (72%) or tumors with unknown grade (20%), stratified survival analysis was performed for these subgroups. For low-grade tumors, patients in the CGH group had significantly worse survival than those in the CGL group (log-rank $P < .017$; Cox proportional hazards model HR 5.61 [1.13–27.92], $P = .035$; 3-year overall survival CGL versus CGH; 99% vs. 94%). Similarly, for patients with unknown grade, the CGH group had significantly worse survival than the CGL group (log-rank $P = .017$; Cox proportional hazards model HR 14.07 [1.72–114.90], $P = .001$; 3-year overall survival CGL versus CGH; 93% vs. 56%).

Many patients in the general population use over-the-counter proton pump inhibitors (PPIs), which may falsely elevate CgA levels if not stopped before testing.[28] To evaluate this concern, we reanalyzed our data after restricting analysis to patients that had no comorbidities. CgA levels continued to be independently

Table 1
Sociodemographic and clinicopathologic characteristics stratified by CgA level.

Characteristic	N = 445	CGL (352)	CGH (93)	P value
Age (years), n (%)				
<40	29 (6)	26 (7)	3 (3)	.134
40–59	193 (43)	157 (45)	36 (39)	
60+	223 (50)	169 (48)	54 (58)	
Sex, n (%)				
Male	203 (46)	157 (45)	46 (49)	.403
Female	242 (54)	195 (55)	47 (51)	
Charlson-Deyo Score, n (%)				
0	331 (74)	272 (77)	59 (63)	.016
1	80 (18)	58 (16)	22 (24)	
2+	34 (8)	22 (6)	12 (13)	
Race, n (%)				
Non-Hispanic White	356 (81)	280 (81)	76 (83)	.804
Black	46 (10)	37 (11)	9 (10)	
Hispanic White	13 (3)	10 (3)	3 (3)	
NA/PI/Asian/Other	23 (5)	20 (6)	3 (3)	
Insurance, n (%)				
Private insurance	238 (54)	189 (54)	49 (53)	.214
Government	192 (44)	148 (43)	44 (47)	
Not insured	10 (2)	10 (3)	0 (0)	
Facility type, n (%)				
Nonacademic	103 (25)	77 (24)	26 (29)	.305
Academic	313 (75)	249 (76)	64 (71)	
Tumor size, mm				
Median (IQR)	14 (11–17)	14 (10.5–17)	15 (11–17)	.952
Tumor size, n (%)				
0.1–1 cm	110 (25)	88 (25)	22 (24)	.789
>1–2 cm	335 (75)	264 (75)	71 (76)	
Clinical node status, n (%)				
Negative	355 (80)	293 (83)	62 (67)	.001
Positive	28 (6)	16 (4)	12 (13)	
Unknown	62 (14)	43 (12)	19 (20)	
Pathologic node status, n (%)				
Negative	247 (55)	215 (61)	32 (34)	<.001
Positive	49 (11)	36 (10)	13 (14)	
Unknown	149 (33)	101 (29)	48 (52)	
No. of lymph nodes examined				
Median (IQR)	3 (0–11)	3 (0–12)	1 (0–9)	.078
Grade, n (%)				
Low	321 (72)	274 (78)	47 (50)	<.001
Intermediate	32 (7)	23 (6)	9 (10)	
High	3 (1)	1 (<1)	2 (2)	
Unknown	89 (20)	54 (15)	35 (38)	
Lymphadenectomy, n (%)				
No	149 (33)	101 (29)	48 (52)	<.001
Yes	296 (66)	251 (71)	45 (48)	
Surgical resection, n (%)				
None	85 (19)	57 (16)	28 (30)	.01
Enucleation	41 (9)	34 (10)	7 (5)	
Pancreatectomy	319 (72)	261 (74)	58 (62)	

Note: Chi-square test for categorical variables; Kruskal-Wallis rank test for continuous variables.
IQR, interquartile range.

Table 2
Predictors of overall survival for small pancreatic neuroendocrine tumors—Cox proportional hazards model.

Characteristic (N = 274)	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years), n (%)				
<40	1 <referent>			
40–59	0.70 (0.08–6.01)	.747		
60+	1.24 (0.16–9.67)	.84		
Sex, n (%)				
Male	1 <referent>			
Female	0.50 (0.18–1.38)	.184		
Charlson-Deyo Score, n (%)				
0	1 <referent>			
1	1.22 (0.33–4.44)	.762		
2+	2.41 (0.66–8.76)	.183		
Race, n (%)				
Non-Hispanic White	1 <referent>			
Black	1.17 (0.26–5.23)	.837		
Hispanic White	1.68 (0.21–13)	.617		
NA/PI/Asian/Other	1.53 (0.20–11.81)	.681		
Insurance, n (%)				
Private insurance	1 <referent>		1 <referent>	
Government	3.88 (1.25–12.06)	.019	3.35 (1.02–11.00)	.045
Not insured	–		–	
Site				
Head	1 <referent>			
Body	0.69 (0.18–2.61)	.584		
Tail	0.24 (0.05–1.11)	.068		
Overlapping	0.49 (0.13–1.87)	.299		
Facility type				
Nonacademic	1 <referent>			
Academic	1.88 (0.42–8.33)	.406		
Tumor size				
0.1–1 cm	1 <referent>			
>1–2 cm	2.07 (0.47–9.11)	.336		
Clinical node status				
Negative	1 <referent>		1 <referent>	
Positive	5 (1.28–19.52)	.021	2.90 (0.60–13.96)	.185
Unknown	4.52 (1.52–13.49)	.007	5.14 (1.35–19.53)	.016
Grade				
Low	1 <referent>		1 <referent>	
Intermediate	2.3 (0.28–19.21)	.441	1.24 (0.13–11.95)	.852
High	168.72 (16.12–1765.77)	<.001	29.65 (2.13–413.26)	.012
Unknown	5.27 (1.82–15.27)	.002	1.57 (0.41–5.96)	.505
Lymphadenectomy				
No	1 <referent>		1 <referent>	
Yes	0.25 (0.09–0.70)	.037	0.55 (0.14–2.15)	.386
Surgical resection				
No	1 <referent>		1 <referent>	
Yes	0.34 (0.12–0.94)	.037	0.72 (0.15–3.36)	.679
CgA level				
Low	1 <referent>		1 <referent>	
High	12.54 (4.03–39.07)	<.001	7.22 (2.10–24.80)	.002

prognostic in this subgroup analysis (Cox proportional hazards model: CGH versus CGL [referent]: HR 19.76, 95% CI 3.00–130.36, $P = .002$). To address the possibility of institutional variation in the performance of CgA assay, we determined if there was evidence of clustering using mixed-effect generalized linear regression model. Introduction of random effects in this model (ie, clustering by facility/presumably by assay) did not improve the generalized linear model (LR test versus linear model: $\chi^2[01] = 0.64$, $P = .212$). The fixed effects in this model were estimated by patient comorbidities, grade, and clinical nodal status. This analysis fails to show any evidence of institutional variation in the performance of CgA assay presuming each institution used a preferred type of assay.

To determine if the addition of clinical nodal status or grade to CgA grouping will improve prognostic utility, we compared nested Cox proportional hazards models (Table SIV). Models incorporating CgA grouping alone had excellent prognostic value (Harrell's C-index 0.82) that only marginally improved with the addition of clinical nodal status or grade.

On multivariate analysis, surgical resection was not associated with overall survival. To explore this further, the effect of resection stratified by a CgA subgroup was evaluated. In the CGL group 295 of 352 patients (84%) underwent surgical resection, whereas in the CGH group 65 of 93 patients (67%) underwent surgical resection. There was a significant difference in survivor functions (log-rank $P < .001$) when patients were stratified into 4 categories, namely: (1) no surgical resection and CGL (3-year OS 92%), (2) surgical resection and CGL (3-year OS 99%), (3) no surgical resection and CGH (3-year OS 50%), and (4) surgical resection and CGH (3-year OS 85%). Figure 3 demonstrates that surgical resection mostly benefits patients in the CGH subgroup.

Discussion

This study evaluates the utility of pretreatment measurement of CgA levels in small localized PNETs. Using statistical modeling,[27] the study identifies an optimal cut-point of 420 ng/mL, which dichotomized the patients into 2 prognostic subgroups. Further, we

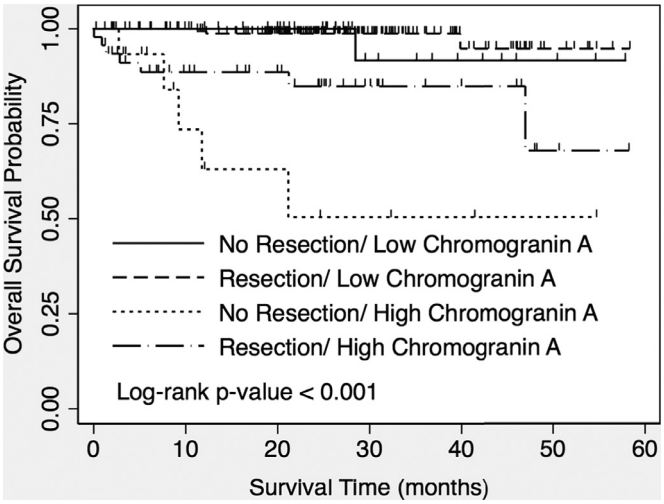

Fig. 3. Kaplan-Meier overall survival plots for patients with small (≤2 cm) pancreatic neuroendocrine tumors (PNETs) stratified by Chromogranin A (CgA) category and resection status. Chromogranin A low (CGL; CgA level ≤420 ng/mL) and chromogranin A high (CGH; CgA level >420 ng/mL). Patients undergoing enucleation are included as resected for this plot. Equality of survival functions tested using the log-rank test.

find that categorization of patients in this manner has prognostic value independent of grade and nodal status. The findings of this study have potential implications in clinical practice.

Predicting biologic behavior of small PNETs has been a subject of significant debate. The controversy stems from conflicting reports in the literature, some of which demonstrate lack of distant metastases for PNETs <2 cm, whereas others demonstrate a 5%–8% chance of distant metastases.[14,15] Even tumors measuring 1–2 cm have a significant chance of nodal metastases.[29] A nodal metastases rate of up to 11% was noted in the present study. This is likely an underestimation because 28% of the patients either did not undergo surgical resection or had enucleation only and thus no pathologic nodal assessment was available for those patients. Most PNETS ≤2 cm are indolent compared with those >2 cm. However, given the findings in the present study as well as prior studies, it seems that there is a group of patients with PNETs ≤2 cm who may benefit from surgical intervention.

Grade has prognostic value but cannot differentiate benign from malignant tumors (characterized by local invasion, nodal, or distant metastases).[29] The assessment of grade on preoperative fine-needle aspirates is also problematic and these data are sparse.[30] For proper classification, at least 40 fields (at 400X magnification) should be evaluated for mitosis and at least 2,000 cells should be assessed for Ki-67 to assign grade, according the WHO and European Neuroendocrine Tumor Society classification.[6] Thus, for a significant number of patients, preoperative grade either cannot be assessed reliably or remains unknown. These observations limit the utility of grade in decision-making regarding surgery versus observation. The present study demonstrates that pretreatment CgA levels have prognostic value independent of grade and clinical nodal status. Even though this study shows that addition of grade or clinical nodal status provides additional prognostic information, the authors believe that the uncertainty of grade determination on preoperative biopsy, and inconsistencies in clinical nodal status assessment, limit routine incorporation of clinical nodal status or grade in preoperative decision-making at present.

Contrary to our findings, a recent study analyzing patients with small PNETs from the NCDB from 1998 to 2012 concluded that elevated CgA levels do not appear to affect survival.[31] In that study, CgA levels were analyzed as categorical variables and the cutoff was arbitrarily defined at 100ng/mL. In contrast, the CgA cutoff in the present study was defined using a well-established statistical approach. We demonstrate that when the patients are dichotomized using a much higher cutoff of 420ng/mL, CgA levels have excellent prognostic utility (Harrell's C-index 0.82).

Apart from CgA, there are several other blood-based prognostic biomarkers under development (reviewed elsewhere[32]). None of these studies specifically focus on small PNETs. However, development of prognostic biomarkers in more advanced disease may also prove to be useful for small PNETs. Some of these include neurokinin, neutrophil-to-lymphocyte ratio, neuron-specific enolase, stromal cell-derived factor 1 alpha (SDF-1a), interleukin-8 (IL-8), and soluble vascular endothelial growth factor receptor 3 (sVEGFR-3). Of note, a gene-expression–based molecular signature, the NETest score, has prognostic utility and is undergoing prospective validation.[33] These potential prognostic markers need to be validated in prospective studies, especially for patients with small PNETs, before clinical use.

There are inherent limitations in the interpretation of the study because of its retrospective design. The follow-up period for this cohort of patients is somewhat limited but the median follow-up is comparable to other studies on the subject. Furthermore, the NCDB does not record disease-specific survival, information on recurrence of disease, or disease-free interval. These would add a level of detail to the analysis in this study but are unlikely to alter the interpretation of the data presented. The observation that CgA levels were associated with increasing grade and positive nodal status provides intermediate end-points for prediction of biologic behavior of the PNETs and provides internal validity to the study observations. Bias that might lead to surgical resection (eg, patient performance status, tumor appearance on imaging, and family history of neuroendocrine disorders) may not be completely captured in the database. Therefore, any conclusions regarding the benefit of surgical resection in a certain subgroup should be interpreted with caution. Pathologic nodal status was missing for a significant number of patients, which is known to have prognostic value and could confound the association between CgA and survival. Additional analyses demonstrated that although lymphadenectomy was less prevalent in the CGH group, it does not independently drive the survival association between the 2 groups.

Beyond the limitations of the study design, falsely elevated levels of CgA have been reported in patients using PPIs, those with renal or liver failure, those with hypertension, and those with chronic gastritis.[34] Because we do not have any information on these variables, it is unclear what percentage of patients may have had falsely elevated CgA levels. Because the association of PPI and false elevation of CgA is widely known, most physicians stop PPIs before testing. When we controlled for comorbidities on subset analysis, CgA levels continued to be prognostic after excluding patients with preexisting conditions, suggesting that in the appropriate clinical context, CgA levels can be used to guide management. External validation of the prognostic significance of CgA levels should be performed in future studies. Assay-dependent variation in the diagnostic utility of CgA levels has been reported in the literature.[35–38] This is largely attributable to the variation in the *diagnostic* cutoffs recommended by the vendors of these commercial tests, which are not relevant to the present study. Furthermore, a critical review of the literature demonstrates a high degree of correlation ($r > 0.80$) between various commercial tests. Consistent with the literature, a subset analysis failed to show any evidence of institutional variation in the performance of CgA assay presuming each institution used a preferred type of assay. Serum CgA levels are easily obtained from a peripheral blood draw and many labs across the United States routinely perform an enzyme-linked immunosorbent assay that has a very small biological variation with a coefficient of variation of 16.3%.[16] For a

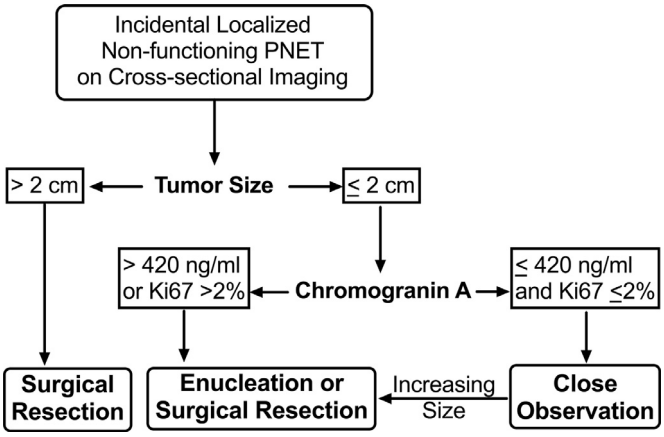

Fig. 4. Management algorithm. A simplified and practical algorithm for the management of incidentally discovered pancreatic neuroendocrine tumors (PNETs) is presented. (Recommendation for surgical resection for PNETs >2cm is based on the high incidence of nodal metastases.)[39]

420 ng/mL cutoff, this would translate to a range of 353 ng/mL to 487ng/mL.

Despite these limitations, the study has important implications for clinical practice. A simplified and practical algorithm for clinical implementation is presented in Fig. 4. CgA levels can be used to predict biologic behavior of small NF-PNETs. If CgA levels are greater than 420 ng/mL, surgical resection should be strongly considered. For the majority of patients, these levels will be 420 ng/mL or less. For these patients, close observation could be considered. This decision must be individualized based on the age of the patient, location of the tumor, extent of resection needed, patient comorbidities, and anticipated compliance with a surveillance regimen.

Acknowledgments

This study used the NCDB. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the American College of Surgeons and the Commission on Cancer in the creation of the NCDB. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed or the conclusions drawn from these data by the authors.

Laleh G. Melstrom was supported by the National Cancer Institute of the National Institutes of Health under award number NIH 5K12CA001727-20. The content is solely the responsibility of Laleh Melstrom and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.10.018.

References

1. Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol*. 2008;19:1727–1733.
2. Halfdanarson TR, Rubin J, Farnell MB, Grant CS, Petersen GM. Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors. *Endocr Relat Cancer*. 2008;15:409–427.
3. Bilimoria KY, Tomlinson JS, Merkow RP, et al. Clinicopathologic features and treatment trends of pancreatic neuroendocrine tumors: analysis of 9,821 patients. *J Gastrointest Surg*. 2007;11:1460–1467 ; discussion 1467–9.
4. Bilimoria KY, Talamonti MS, Tomlinson JS, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. *Ann Surg*. 2008;247:490–500.
5. Nissen NN, Kim AS, Yu R, et al. Pancreatic neuroendocrine tumors: presentation, management, and outcomes. *Am Surg*. 2009;75:1025–1029.
6. Falconi M, Eriksson B, Kaltsas G, et al. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinology*. 2016;103:153–171.
7. NCCN Clinical Practice Guidelines in Oncology version 3.2018. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed November 12, 2018.
8. Gaujoux S, Partelli S, Maire F, et al. Observational study of natural history of small sporadic nonfunctioning pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab*. 2013;98:4784–4789.
9. Lee LC, Grant CS, Salomao DR, et al. Small, nonfunctioning, asymptomatic pancreatic neuroendocrine tumors (PNETs): role for nonoperative management. *Surgery*. 2012;152:965–974.
10. Strosberg JR, Cheema A, Kvols LK. Stage I nonfunctioning neuroendocrine tumors of the pancreas: surgery or surveillance? *J Clin Oncol*. 2011;29(Suppl4):349.
11. Sadot E, Reidy-Lagunes DL, Tang LH, et al. Observation versus resection for small asymptomatic pancreatic neuroendocrine tumors: a matched case-control study. *Ann Surg Oncol*. 2016;23:1361–1370.
12. Regenet N, Carrere N, Boulanger G, et al. Is the 2-cm size cutoff relevant for small nonfunctioning pancreatic neuroendocrine tumors: a French multicenter study. *Surgery*. 2016;159:901–907.
13. Sharpe SM, In H, Winchester DJ, Talamonti MS, Baker MS. Surgical resection provides an overall survival benefit for patients with small pancreatic neuroendocrine tumors. *J Gastrointest Surg*. 2015;19:117–123 ; discussion 123.
14. Cherenfant J, Stocker SJ, Gage MK, et al. Predicting aggressive behavior in nonfunctioning pancreatic neuroendocrine tumors. *Surgery*. 2013;154:785–791 discussion 791–3.
15. Haynes AB, Deshpande V, Ingkakul T, et al. Implications of incidentally discovered, nonfunctioning pancreatic endocrine tumors: short-term and long-term patient outcomes. *Arch Surg*. 2011;146:534–538.
16. Braga F, Ferraro S, Mozzi R, Dolci A, Panteghini M. Biological variation of neuroendocrine tumor markers Chromogranin A and neuron-specific enolase. *Clin Biochem*. 2013;46:14851.
17. Panzuto F, Severi C, Cannizzaro R, et al. Utility of combined use of plasma levels of Chromogranin A and pancreatic polypeptide in the diagnosis of gastrointestinal and pancreatic endocrine tumors. *J Endocrinol Invest*. 2004;27:6–11.
18. Wang YH, Yang QC, Lin Y, Xue L, Chen MH, Chen J. Chromogranin A as a marker for diagnosis, treatment, and survival in patients with gastroenteropancreatic neuroendocrine neoplasm. *Medicine (Baltimore)*. 2014;93:e247.
19. Campana D, Nori F, Piscitelli L, et al. Chromogranin A: is it a useful marker of neuroendocrine tumors? *J Clin Oncol*. 2007;25:1967–1973.
20. Nikou GC, Marinou K, Thomakos P, et al. Chromogranin A levels in diagnosis, treatment and follow-up of 42 patients with non-functioning pancreatic endocrine tumours. *Pancreatology*. 2008;8:510–519.
21. Modlin IM, Gustafsson BI, Moss SF, Pavel M, Tsolakis AV, Kidd M. Chromogranin A—biological function and clinical utility in neuro endocrine tumor disease. *Ann Surg Oncol*. 2010;17:2427–2443.
22. Lerro CC, Robbins AS, Phillips JL, Stewart AK. Comparison of cases captured in the national cancer data base with those in population-based central cancer registries. *Ann Surg Oncol*. 2013;20:1759–1765.
23. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613–619.
24. Ramage JK, Davies AH, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. *Gut*. 2005;54(Suppl 4) iv1–16.
25. Plockinger U, Rindi G, Arnold R, et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). *Neuroendocrinology*. 2004;80:394–424.
26. Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch*. 2006;449:395–401.
27. Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. *Computational Statistics & Data Analysis*. 1999;30:253–270.
28. Korse CM, Muller M, Taal BG. Discontinuation of proton pump inhibitors during assessment of Chromogranin A levels in patients with neuroendocrine tumours. *Br J Cancer*. 2011;105:1173–1175.
29. Hashim YM, Trinkaus KM, Linehan DC, et al. Regional lymphadenectomy is indicated in the surgical treatment of pancreatic neuroendocrine tumors (PNETs). *Ann Surg*. 2014;259:197–203.
30. Figueiredo FA, Giovannini M, Monges G, et al. EUS-FNA predicts 5-year survival in pancreatic endocrine tumors. *Gastrointest Endosc*. 2009;70:907–914.

31. Mirkin KA, Hollenbeak CS, Wong J. Impact of Chromogranin A, differentiation, and mitoses in nonfunctional pancreatic neuroendocrine tumors </= 2 cm. *J Surg Res*. 2017;211:206–214.
32. Chan DL, Clarke SJ, Diakos CI, et al. Prognostic and predictive biomarkers in neuroendocrine tumours. *Crit Rev Oncol Hematol*. 2017;113:268–282.
33. Genc CG, Jilesen APJ, Nieveen van Dijkum EJM, et al. Measurement of circulating transcript levels (NETest) to detect disease recurrence and improve follow-up after curative surgical resection of well-differentiated pancreatic neuroendocrine tumors. *J Surg Oncol*. 2018;118:37–48.
34. Pregun I, Herszenyi L, Juhasz M, et al. Effect of proton-pump inhibitor therapy on serum Chromogranin A level. *Digestion*. 2011;84:22–28.
35. Brehm Hoej L, Parkner T, Soendersoe Knudsen C, Gronbaek H. A comparison of three Chromogranin A assays in patients with neuroendocrine tumours. *J Gastrointestin Liver Dis*. 2014;23:419–424.
36. Popovici T, Moreira B, Schlageter MH, Bories PN. Automated two-site immunofluorescent assay for the measurement of serum Chromogranin A. *Clin Biochem*. 2014;47:87–91.
37. Leon A, Torta M, Dittadi R, et al. Comparison between two methods in the determination of circulating Chromogranin A in neuroendocrine tumors (NETs): results of a prospective multicenter observational study. *Int J Biol Markers*. 2005;20:156–168.
38. Stridsberg M, Eriksson B, Oberg K, Janson ET. A comparison between three commercial kits for Chromogranin A measurements. *J Endocrinol*. 2003;177:337–341.
39. Network NCC. NCCN Guidelines Neuroendocrine and Adrenal Tumors (Version 2.2018). 2018; https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine_blocks.pdf. Accessed September 28, 2018.