Journal of Gastrointestinal Surgery (2019) 23:651–658
https://doi.org/10.1007/s11605-018-04080-1

2018 SSAT PLENARY PRESENTATION

Predictive Value of Chromogranin A and a Pre-Operative Risk Score to Predict Recurrence After Resection of Pancreatic Neuroendocrine Tumors

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Received: 1 June 2018 / Accepted: 12 December 2018 / Published online: 18 January 2019

Abstract

Intro Chromogranin A (CgA) may be prognostic for patients with neuroendocrine tumors; however, the clinical utility of this test is unclear.

Methods Patients undergoing resection for pancreatic neuroendocrine tumors (pNET) were selected from the eight institutions of the US Neuroendocrine Tumor Study Group database. Cox regression was used to identify pre-operative variables that predicted recurrence-free survival (RFS), and those with $p < 0.1$ were included in a risk score. The risk score was tested in a unique subset of the overall cohort.

Results In the entire cohort of 287 patients, median follow-up time was 37 months, and 5-year RFS was 73%. Cox regression analysis identified four variables for inclusion in the risk score: CgA > 5x ULN (HR 4.3, $p = 0.01$), tumor grade 2/3 (HR 3.7, $p = 0.01$), resection for recurrent disease (HR 6.2, $p < 0.01$), and tumor size > 4 cm (HR 4.5, $p = 0.1$). Each variable was assigned 1 point. Risk-score testing in the unique validation cohort of 63 patients revealed a 95% negative predictive value for recurrence in patients with zero points.

Discussion This simple pre-operative risk scoring system resulted in a high degree of specificity for identifying patients at low-risk for tumor recurrence. This test can be utilized pre-operatively to aid informed decision-making.

Keywords Chromogranin A · Pancreatic neuroendocrine tumor · Recurrence · Risk score

This work was accepted for plenary oral presentation on June 3, 2018, at the Society for Surgery of the Alimentary Tract Annual Meeting in Washington, D.C.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11605-018-04080-1) contains supplementary material, which is available to authorized users.

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Introduction

Pancreatic neuroendocrine tumors (pNET) are rare neoplasms of the pancreas arising from islet of Langerhans cells. These tumors can be subdivided into functional or non-functional tumors, based on secretion of endocrine hormones including gastrin, insulin, glucagon, or vasoactive-intestinal peptide (VIP). Surgical resection offers the only potential curative therapy, and generally, patients have a favorable prognosis, even in the setting of metastatic or recurrent tumors if all disease sites can be resected. [1–3]

Despite excellent long-term survival, regional and distant recurrence after pNET resection is common, occurring in 25% of all patients, and often necessitates additional interventions, surgeries, and treatments. [4–6] Most prior studies that assessed risk factors for recurrence have largely focused on pathologic features such as lymph node involvement or perineural invasion. [1, 4, 6–8] While pathologic risk factors are useful in determining prognosis, the need for adjuvant therapy, and frequency of post-operative surveillance, they are not available to help guide pre-operative decision-making. Specifically, pre-operative risk stratification would be useful to guide surgical planning (e.g., resection vs. enucleation), determine utility of additional pre-operative imaging (e.g., somatostatin-receptor-based imaging), and to guide decisions regarding neoadjuvant therapies.

Approximately, 70% of pNET tumors are hyper-secretors of the peptide chromogranin A (CgA), which can be readily measured in serum blood samples. [9] Previous studies have suggested that CgA levels may have prognostic value for patients with neuroendocrine tumors. [10–12] However, these results are not consistent across all studies, and the clinical utility of pre-operative CgA measurement is unclear. [13]

Due to a lack of data and poor understanding of pre-operative risk factors for recurrence after resection for pNET, this study sought to evaluate patient risk for recurrence based on chromogranin A and other pre-operative variables in order to aid decision-making regarding pre-operative imaging, neoadjuvant therapy, and surgical approach.

Methods

Data Source

The study sample consists of patients from the United States Neuroendocrine Tumor Study Group (US-NETSG) database. This database consists of pooled data obtained from retrospective chart review from eight academic, tertiary care institutions across the USA. Each institution granted IRB approval for this study.

Patient Population

Adult patients ≥ 18 years old who underwent curative-intent resection of non-functional or functional pNET between January 2000 and July 2016 were included. Patients with synchronous metastases or tumor recurrence were included if the intent of surgery was curative, namely resection of all disease sites.

In order to assess risk for tumor recurrence, patients were excluded if they underwent an R2 resection, with exception given to patients undergoing a planned two or three staged operation where curative intent resection of all disease sites was eventually obtained. In order to assess predictive value of chromogranin A, patients without pre-operative measurement of chromogranin A were excluded. Chromogranin A levels can be falsely elevated by proton pump inhibitor (PPI) use and impaired renal function. [14–16] Therefore, to assess predictive value of CgA, patients were also excluded if they were on pre-operative antacid therapy, dialysis, had acute renal failure at time of operation, or had baseline creatinine > 1.5 mg/dL.

Chromogranin A Testing

For the eight institutions in this study, serum specimens for chromogranin A testing were sent to one of three locations: (1) Mayo Clinic Laboratory (Rochester, MN, USA), (2) Quest Diagnostics Nichols Institute (San Juan Capistrano, CA, USA), or (3) Associated Regional and University Pathologist (ARUP) Laboratories, (Salt Lake City, UT, USA). The normal reference range for CgA varied between these three laboratories, and varied over time within each laboratory (See Supplemental Table 1). This fact precluded the ability to analyze serum CgA levels as a continuous variable, and thus, three categories were created as follows to allow comparisons between patients: within normal range, 1–5x upper limit normal (ULN), and > 5x ULN. This methodology was consistent with prior studies. [10, 11, 17] Each patient's CgA value was coded into these categories using the CgA reference range corresponding to the appropriate reference lab and date of surgery.

Survival Analysis

Survival was measured from the time of resection until last clinical follow-up, death from any cause (overall survival), or radiographic or pathologic evidence of tumor recurrence (recurrence-free survival). Evidence of recurrence was obtained by searching provider notes, radiology reports, and pathology reports occurring after the date of surgery at both the index institution, and outside institutions when available. Tumor grade and tumor size used

for survival analysis were obtained from the final pathology report. Survival curves were generated for the overall cohort using the Kaplan–Meier method. Survival curves were then compared across the three patient groups based on chromogranin A levels using the log-rank test, with significance defined as $p < 0.05$.

Recurrence Risk-Score Development

A stratified random sample aimed at sampling 75% of the patient cohort was selected for the risk-score creation patient subset, with the remaining 25% of patients used for risk-score validation. Strata for randomization included variables of anticipated clinical relevance including CgA level, tumor grade, recurrent versus primary tumor, functional versus non-functional tumors, and presence of multifocal tumors (either primary or metastatic).

In the risk-score creation cohort, Cox proportional hazards modeling was carried out to identify independent associations with RFS, and variables with $p < 0.1$ were selected for inclusion in the risk score to predict tumor recurrence. To assess ability of risk score to discriminate probability of RFS, Kaplan–Meier Survival curves were compared according to total risk-score points for patients in both the risk-score creation cohort and risk-score validation cohort. Next, to assess predictive value of the risk score among unique patients, logistic regression was carried out in the risk-score validation cohort, and area under the receiver operating characteristics (ROC) curve was determined. To assess for the possibility of this confirmation bias, the frequency of post-operative surveillance imaging and length of follow-up were compared between the different risk-score groups.

Given that patients with poorly differentiated or high-grade tumors, recurrent disease, and metastatic disease inherently represent a higher-risk subset, Cox proportional hazards modeling was repeated after excluding these patients. After these exclusions, only 181 patients remained with data on tumor grade, and there were 16 recurrences. Therefore, a single Cox model was used for the entire cohort, rather than stratifying into two groups for a second risk-score creation and validation.

Table 1 Demographics and tumor characteristics

	$n = 287$
Age, median (IQR)	58 (47–66)
Gender (% female)	149 (52%)
Race, *n* (%)	
Caucasian	225 (79%)
African-American	15 (5%)
Asian	20 (7%)
Other/unknown	27 (9%)
ASA class ($n = 281$)	
1–2	140 (50%)
3	138 (49%)
4	3 (1%)
Genetic syndrome	
MEN-1	20 (7%)
vHL, NF, other	4 (1%)
Tumor functionality	
Non-functional	257 (90%)
Insulinoma	19 (7%)
Glucagonoma	5 (2%)
Other	6 (2%)
Tumor location	
Pancreas only	250 (86%)
Pancreas + synchronous mets.	20 (7%)
Locally recurrent	9 (3%)
Metastatic recurrent	8 (3%)
Tumor size, median (IQR)	2.4 cm (1.5–4.0)
Tumor grade ($n = 230$)	
Low grade (G1)	155 (67%)
Intermediate grade (G2)	67 (29%)
High grade (G3)	8 (3%)
Pre-operative CgA	
Normal	176 (61%)
1–5x ULN	85 (30%)
> 5x ULN	26 (9%)
Final resection margin ($n = 285$)	
R0	235 (82%)
R1	50 (18%)

MEN-1 multiple endocrine neoplasia type 1, *vHL* von-Hippel Lindau, *NF* Neurofibromatosis, *mets.* metastases, *CgA* chromogranin A, *ULN* upper limit of normal

Results

Patient and Tumor Characteristics

A total of 287 patients underwent curative intent resection for primary or recurrent pNET and met inclusion and exclusion criteria. Patient demographics and tumor features are represented in Table 1. The majority of patients ($n = 257$, 90%) had non-functional tumors and most also had isolated primary tumors of the pancreas ($n = 250$, 86%). Twenty patients had synchronous liver metastases, and 17 had local or distant recurrence of a pancreas primary tumor. All patients were treated with curative intent surgery of all disease sites. One hundred thirteen (39%) patients had elevated CgA levels, but only a small proportion of these patients ($n = 27$, 9%) had significant elevation to above five times the upper limit of normal for the assay.

Surgical Procedures

For patients undergoing resection of their pancreatic tumor, distal pancreatectomy was the most common operation performed ($n = 158$), followed by pancreaticoduodenectomy ($n = 82$), and enucleation ($n = 26$). Eight patients underwent central pancreatectomy, and six underwent total pancreatectomy. Twenty-five patients were treated for synchronous or recurrent liver metastases. These surgeries included wedge resections ($n = 14$), one or two segment hepatectomy ($n = 10$), or major hepatectomy of ≥ 3 segments ($n = 5$). Three of these patients had additional intra-operative ablations performed.

Survival and Recurrence

Median follow-up time was 37 months (IQR 15–62 months); there were 17 observed deaths, and 55 patients (19%) experienced tumor recurrence. For all 287 patients, 5-year overall survival (OS) was 92%, and 5-year recurrence-free survival (RFS) was 73%. Marked elevations of CgA were associated with significantly worse OS and RFS. For patients with CgA > 5x ULN, 5-year OS was 75% compared to 91% for CgA 1–5x ULN, and 96% in those with normal CgA levels ($p = 0.003$). In addition, 5-year RFS was 54% for those with CgA > 5x ULN compared to those with mild elevation or normal CgA and 70% and 77% for those with mild elevation or normal CgA, respectively (Fig. 1; $p = 0.03$).

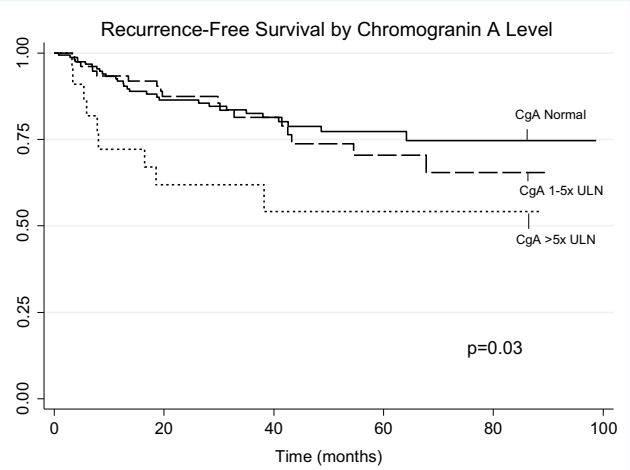


Fig. 1 Kaplan–Meier recurrence-free survival stratified by chromogranin A level. Kaplan–Meier recurrence-free survival (RFS) curves for patients with normal chromogranin A (CgA) (solid line), mildly elevated CgA to 1–5x upper limit of normal (ULN) (dashed line), and those with marked CgA elevation to > 5x ULN (dotted line). Significantly worse 5-year survival seen for markedly elevated CgA with 5-year RFS was 54%, compared to 70% and 77% for CgA 1–5x ULN and CgA normal, respectively

Risk-Score Creation

A stratified random sample ($n = 224$) of the overall cohort was selected for risk-score creation, with the remaining patients ($n = 63$) used for risk-score validation. In the risk-score creation cohort, Cox PH modeling was carried out to identify independent associations with RFS; results are depicted in Table 2. Using a cutoff of $p < 0.1$, four variables met criteria for inclusion in the risk score, including (1) tumor grade 2 or 3, (2) CgA > 5x upper limit of normal, (3) surgery for tumor recurrence, and (4) tumor size ≥ 4.0 cm. Given the wide overlap of 95% confidence intervals for these four variables (Table 2), and to create a simplified risk-score system, each of the four variables was assigned 1 point, for an overall risk-score range of 0–4 points.

For patients in the risk-score development cohort, we next tested for associations between chromogranin A and other risk factors in the final risk-score system that may indicate redundancy. Average tumor size was significantly larger in patients with markedly elevated CgA levels (5.2 cm vs. 2.8 cm for normal CgA and 4.0 for CgA 1–5x ULN, $p < 0.01$; Supplemental Table 2). There was not a significant association between chromogranin level and tumor grade. Patients with significant elevations of CgA were more likely to have recurrent disease or synchronous metastases compared to patients with mild elevation or normal CgA (Supplemental Table 2). However, out of 23 patients with CgA > 5x ULN, 11 had small tumors less than 4 cm, 9 had low-grade tumors, and 15 had primary tumors only. This indicated that marked elevations of CgA were often present without other high-risk features in the risk-score model, and inclusion of CgA was not redundant with the other risk factors.

Within the risk-score development cohort, patient stratification into low-risk (0 points, $n = 111$), intermediate-risk (1 point, $n = 71$), and high-risk (≥ 2 points, $n = 42$) groups resulted in significant survival discrimination between groups (5-year RFS for low risk 96%, intermediate 63%, and high-risk 39%, $p < 0.001$; Fig. 2, upper portion). Repeating this survival analysis within the unique validation cohort revealed similar trends, with 5-year RFS of 96% for low risk, 62% for intermediate risk, and 0% for high risk ($p < 0.001$; Fig. 2, lower portion). Risk-score testing in the unique validation cohort of 63 patients resulted in an area under ROC curve of 0.78 (Fig. 3) with 92% specificity, 37% sensitivity, negative predictive value of 87%, positive predictive value of 50%, and overall accuracy of 83%. Among the subset of patients who were low risk for tumor recurrence (risk score of 0 points), the NPV of the risk score for tumor recurrence was 95%.

Imaging surveillance every 3–6 months was more common in patients with higher-risk score (69% for 2–4 points vs. 61% for 1 point vs. 39% for 0 points, $p < 0.01$), while annual surveillance was more common for low-risk patients. There were not substantial differences in the proportion of patients getting

Table 2 Cox proportional hazards modeling for recurrence free survival in risk-score creation cohort and risk-score point assignment

	HR [95% CI]	*p* value	Risk-score points
Age (< 50 reference)			
50–59	0.85 [0.22–3.18]	0.81	
60–69	1.09 [0.34–3.48]	0.89	
> 70	0.74 [0.20–2.73]	0.66	
Tumor functionality			
Non-functional	Reference		
Functional	1.27 [0.41–3.94]	0.68	
Tumor grade			
Low grade (G1)	Reference		
G2 or G3	3.67 [1.34—10.00]	0.01	1 Point
Chromogranin A			
Normal	Reference		
1–5x ULN	0.62 [0.20–1.95]	0.41	
> 5x ULN	4.25 [1.38—13.08]	0.01	1 Point
Tumor category			
Pancreatic primary only	Reference		
Pancreas + synchronous mets.	1.10 [0.29—4.23]	0.89	
Local or distant recurrence	6.22 [2.05—18.83]	< 0.01	1 Point
Tumor size			
< 1.5 cm	Reference		
1.5–2.4 cm	1.61 [0.24—10.83]	0.63	
2.5–3.9 cm	3.65 [0.59—22.62]	0.16	
≥ 4.0 cm	4.51 [0.68—29.87]	0.11	1 Point

ULN upper limit of normal; *mets*. metastases

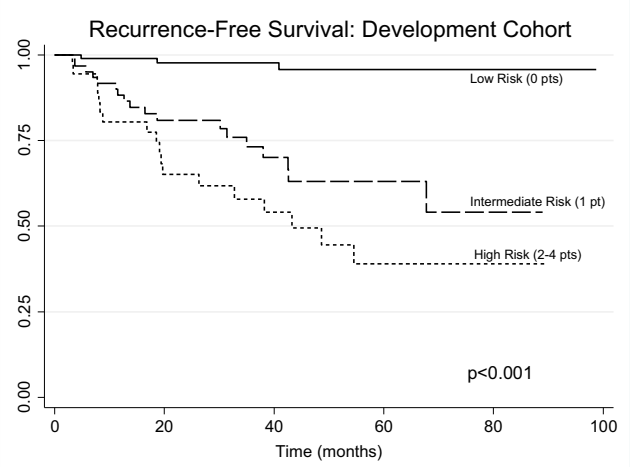
no surveillance, which were 19%, 12%, and 16% for low, intermediate, and high-risk patients, respectively. The mean length of follow-up did not differ significantly according to risk score, and was 42 months for low risk, 38 months for intermediate risk, and 44 months for high risk ($p = 0.42$).

Finally, patients at high risk for recurrence were excluded and a Cox model for RFS was repeated among only those patients with non-metastatic, well-differentiated primary pancreatic tumors. This analysis revealed that only tumor size > 4 cm (HR 8.5 [1.4–52.6], $p = 0.02$), and tumor grade 2 (HR 6.7 [2.1—21.1], $p < 0.001$) were significantly associated with worse survival. Chromogranin A level, patient age, presence of genetic syndrome, and functional tumors were not significantly associated with survival.

Discussion

In this study of patients with pNET, a novel risk scoring system based on variables available pre-operatively was generated. These variables included (1) substantial elevation of chromogranin A level to > 5x the upper limit of normal, (2) intermediate-grade or high-grade tumor (3) large tumor > 4.0 cm, and (4) presence of a recurrent tumor. Risk-stratification for tumor recurrence using this risk-scoring system resulted in high degree of ability to discriminate recurrence-free survival (RFS), with 5-year RFS rates of 39%, 63%, or 96% depending on risk-score group. While the risk-score model did not perform well in positively predicting recurrence, the negative predictive value of having 0 points was 95%, giving clinicians confidence in identifying the majority of pNET patients who will be at a very low risk for tumor recurrence.

The risk score created in this study could be broadly applied to any patient with a pNET undergoing curative intent resection, including those with synchronous metastases or recurrent tumors. A sensitivity analysis of the subset of low-risk patients was carried out examining only those with primary well-differentiated tumors. In this subset, only tumor size > 4 cm and tumor grade 2 were significantly associated with recurrence. This analysis was limited by a small sample size, and given the favorable prognosis of patients with well-differentiated tumors, there were only a small number of recurrence events, both of which decrease the ability to find statistically significant results in the multivariable model. However, this sensitivity analysis suggests that chromogranin A may have more prognostic value in patients with high-grade tumors, metastases, or those being treated for recurrence, and may not informative in patients who are otherwise low risk.



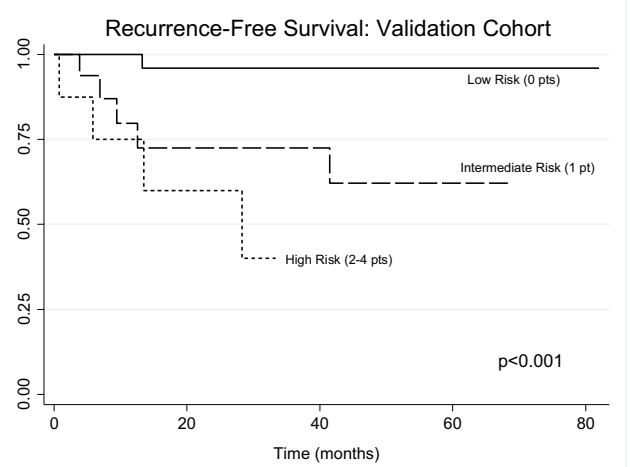


Fig. 2 Kaplan–Meier survival curves by pre-operative risk score. One point in the recurrence risk score given for presence of tumor grade 2/3, tumor > 4 cm, CgA > 5x upper limit of normal, and recurrent tumor. Dividing patients into low risk (0 points, solid line), intermediate risk (1 pt., dashed line), and high risk (2–4 points, dotted line), resulted in significant recurrence-free survival discrimination between the three groups in both the develompent cohort (upper portion) and the unique validation cohort (lower portion)

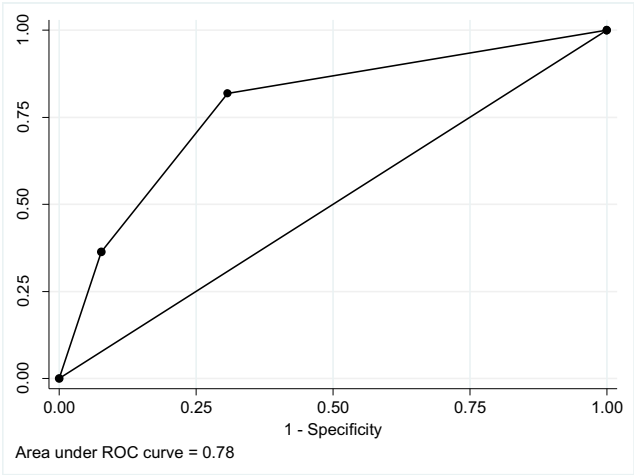


Fig. 3 Receiver operating characteristic curve for predicting tumor recurrence in unique validation cohort using pre-operative risk score. Stratification of 63 unique patients in validation cohort into low risk (0 points), intermediate risk (1 point), or high risk (2–4 points) revealed high specificity of risk-score model for predicting patients at low risk for tumor recurrence after curative intent resection. ROC receiver operating characteristic

This study differs from many prior reports on pNET patients that generated recurrence risk scoring systems in that the current study analyzed only variables available pre-operatively, while most previous studies incorporated post-operative pathologic variables. [4–8, 18–20] Two prior studies have examined pre-operative risk factors. Postlewait and colleagues analyzed 187 patients and found that male gender, tumor size >2 cm, and tumor location in the head or uncinate process were associated with lymph node metastases, which in turn predicted worse disease-free survival. [21] In a small study of 21 patients, Nanno et al. found that CgA and tumor grade were predictive of tumor recurrence, consistent with results from this study. [22] While we did not find that gender or tumor location predicted recurrence, the results from these two smaller studies are consistent with this study in that both tumor size and grade are associated with worse outcomes.

Bilimoria and colleagues reported on a large national sample of over 3000 patients, and developed a prognostic risk score for overall survival based on factors of age, tumor grade, and presence of metastases. [1] While these factors are known pre-operatively, the multivariable analysis used to create the risk-score model incorporated the type of resection and several pathologic outcomes, thereby confounding ability to interpret this as a true pre-operative risk score. Furthermore, the endpoint of the study was overall survival, rather than recurrence.

The utility of a pre-operative risk score may be most evident when considering advances in imaging modalities for neuroendocrine tumors. Most pNET overexpress the somatostatin receptor (SSR), a feature which is exploited by SSR-based imaging modalities such as octreotide scintigraphy (octreotide scans) and newer techniques such as ^{68}Ga-DOTA-peptide PET scans. [23] Traditional MRI and CT scans have a sensitivity of only 50–80% for detecting neuroendocrine tumors. [24] This contrast with sensitivity of 97% and specificity of over 92% for ^{68}Ga-DOTA-peptide PET scans, which also significantly outperforms octreotide scans. However, SSR-based imaging is expensive, not available at all centers, and likely not warranted for all patients. The role in the diagnosis of neuroendocrine tumors is also mostly studies in patients with metastatic disease, and their utility in patients with isolated lesions on CT or MRI is unclear. However, patients at high risk for recurrence may benefit from SSR-based imaging if these adjunct tests can uncover occult disease not seen on CT or MRI, thereby potentially allowing a single, definitive surgery and avoiding recurrence. Further study is needed to evaluate the role of these tests for patients undergoing resection for pNET.

Knowledge of patients' recurrence risk pre-operatively may influence surgical decision-making for the planned resection, for example, choosing enucleation versus formal resection. Furthermore, a recent study by Ricci and colleagues showed that even with radical surgery, subsets of patients with poor prognostic features such as grade 3 tumors are unlikely to achieve a cure. [5] Multimodal therapy therefore has a prominent role in these patients, and pre-operative risk stratification for recurrence may sway providers towards neoadjuvant treatments for a small subset of patients.

This study does have several limitations. First, provider knowledge of high-risk features may have influenced the frequency or duration of post-operative surveillance, which in turn increases the chances of detecting recurrence for high-risk patients. Therefore, there is likely confirmation bias for patients with the tumor risk factors used in our scoring system, and the associations between risk score and recurrence may be an artifact of increased surveillance. Although higher-risk patients did receive more frequent surveillance, the length of follow-up was nearly identical for all patients and most patients received at least annual cross-sectional surveillance imaging. These facts likely minimize the potential for confirmation bias. While tumor grade was included in the recurrence risk score, this information is not always available if biopsies are not obtained or are non-diagnostic. This study is also subject to inherent limitations and biases due to its retrospective nature, and heterogeneity of clinical practices and surgical techniques across the eight institutions is included.

Conclusion

This novel pre-operative risk scoring system appears to be useful in predicting patients that are at low risk for recurrence, and can aid surgeons and clinicians in pre-operative informed decision-making. This simple risk score does not require a nomogram or risk calculator, thereby reducing barriers for use and making integration into a clinical setting straightforward.

Acknowledgements SMW and DEA are supported with the resources and use of facilities at the William S. Middleton Memorial Veterans Hospital, Madison, WI.

Funding Information AVF's position as a research fellow is supported by NIH Surgical Oncology Training Grant (T32 CA090217), and an American College of Surgeons Resident Research Scholarship.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

References

1. Bilimoria KY, Talamonti MS, Tomlinson JS, Stewart AK, Winchester DP, Ko CY, Bentrem DJ. Prognostic Score Predicting Survival After Resection of Pancreatic Neuroendocrine Tumors. Ann Surg. 2008;247:490–500.
2. Saxena A, Chua TC, Chu F, Al-Zahrani A, Morris DL. Optimizing the Surgical Effort in Patients With Advanced Neuroendocrine Neoplasm Hepatic Metastases. Am J Clin Oncol. 2012;35:439–445.
3. Kim MJ, Choi DW, Choi SH, Heo JS, Park HJ, Choi KK, Jang K-T, Sung J-Y. Surgical strategies for non-functioning pancreatic neuroendocrine tumours. Br J Surg. 2012;99:1562–1568.
4. Slagter AE, Ryder D, Chakrabarty B, Lamarca A, Hubner RA, Mansoor W, O'Reilly DA, Fulford PE, Klümpen HJ, Valle JW, McNamara MG. Prognostic factors for disease relapse in patients with neuroendocrine tumours who underwent curative surgery. Surg Oncol. 2016;25:223–228.
5. Ricci C, Casadei R, Taffurelli G, Campana D, Ambrosini V, Pacilio CA, Santini D, Brighi N, Minni F. Is radical surgery always curative in pancreatic neuroendocrine tumors? A cure model survival analysis. Pancreatology. 2018;18:313–317.
6. Ricci C, Casadei R, Taffurelli G, Buscemi S, D'Ambra M, Monari F, Santini D, Campana D, Tomassetti P, Minni F. The role of lymph node ratio in recurrence after curative surgery for pancreatic endocrine tumours. Pancreatology. 2013;13:589–593.
7. Genç CG, Jilesen AP, Partelli S, Falconi M, Muffatti F, van Kemenade FJ, van Eeden S, Verheij J, van Dieren S, van Eijck CHJ, Nieveen van Dijkum EJM. A New Scoring System to Predict Recurrent Disease in Grade 1 and 2 Nonfunctional Pancreatic Neuroendocrine Tumors. Ann Surg. 2018;267:1148–1154.
8. Strosberg JR, Cheema A, Weber JM, Ghayouri M, Han G, Hodul PJ, Kvols LK. Relapse-free survival in patients with nonmetastatic, surgically resected pancreatic neuroendocrine tumors: an analysis of the AJCC and ENETS staging classifications. Ann Surg. 2012;256:321–325.
9. Nobels FR, Kwekkeboom DJ, Coopmans W, Schoenmakers CH, Lindemans J, De Herder WW, Krenning EP, Bouillon R, Lamberts SW. Chromogranin A as serum marker for neuroendocrine neoplasia: comparison with neuron-specific enolase and the alpha-subunit of glycoprotein hormones. J Clin Endocrinol Metab. 1997;82:2622–2628.
10. Shanahan MA, Salem A, Fisher A, Cho CS, Leverson G, Winslow ER, Weber SM. Chromogranin A predicts survival for resected pancreatic neuroendocrine tumors. J Surg Res. 2016;201:38–43.
11. Ekeblad S, Skogseid B, Dunder K, Oberg K, Eriksson B. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. Clin Cancer Res. 2008;14:7798–7803.
12. 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.
13. Qiu W, Christakis I, Silva A, Bassett RL, Cao L, Meng QH, Gardner Grubbs E, Zhao H, Yao JC, Lee JE, Perrier ND. Utility of chromogranin A, pancreatic polypeptide, glucagon and gastrin in the diagnosis and follow-up of pancreatic neuroendocrine tumours in multiple endocrine neoplasia type 1 patients. Clin Endocrinol. 2016;85:400–407.
14. 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.
15. Pregun I, Herszényi L, Juhász M, Miheller P, Hritz I, Patócs A, Rácz K, Tulassay Z. Effect of Proton-Pump Inhibitor Therapy on Serum Chromogranin A Level. Digestion. 2011;84:22–28.

16. Tramonti G, Ferdeghini M, Annichiarico C, Norpoth M, Donadio C, Bianchi R, Bianchi C. Relationship between renal function and blood level of chromogranin A. Ren Fail. 2001;23:449–457.
17. Nikou GC, Marinou K, Thomakos P, Papageorgiou D, Sanzanidis V, Nikolaou P, Kosmidis C, Moulakakis A, Mallas E. Chromogranin a levels in diagnosis, treatment and follow-up of 42 patients with non-functioning pancreatic endocrine tumours. Pancreatology. 2008;8:510–519.
18. Landoni L, Marchegiani G, Pollini T, Cingarlini S, D'Onofrio M, Capelli P, De Robertis R, Davì M V., Amodio A, Impellizzeri H, Malpaga A, Miotto M, Boninsegna L, Crepaz L, Nessi C, Zingaretti CC, Paiella S, Esposito A, Casetti L, Malleo G, Tuveri M, Butturini G, Salvia R, Scarpa A, Falconi M, Bassi C. The Evolution of Surgical Strategies for Pancreatic Neuroendocrine Tumors (Pan-NENs). Ann Surg. 2017. [Epub] Available from: http://www.ncbi.nlm.nih.gov/pubmed/29189384
19. Birnbaum DJ, Turrini O, Vigano L, Russolillo N, Autret A, Moutardier V, Capussotti L, Le Treut Y-P, Delpero J-R, Hardwigsen J. Surgical Management of Advanced Pancreatic Neuroendocrine Tumors: Short-Term and Long-Term Results from an International Multi-institutional Study. Ann Surg Oncol. 2015;22:1000–1007.
20. Tsutsumi K, Ohtsuka T, Fujino M, Nakashima H, Aishima S, Ueda J, Takahata S, Nakamura M, Oda Y, Tanaka M. Analysis of risk factors for recurrence after curative resection of well-differentiated pancreatic neuroendocrine tumors based on the new grading classification. J Hepatobiliary Pancreat Sci. 2014;21:418–425.
21. Postlewait LM, Ethun CG, Baptiste GG, Le N, McInnis MR, Cardona K, Russell MC, Sarmiento JM, Kooby DA, Staley CA, Maithel SK. Pancreatic neuroendocrine tumors: Preoperative factors that predict lymph node metastases to guide operative strategy. J Surg Oncol. 2016;114:440–445.
22. Nanno Y, Toyama H, Matsumoto I, Otani K, Asari S, Goto T, Ajiki T, Zen Y, Fukumoto T, Ku Y. Baseline plasma chromogranin A levels in patients with well-differentiated neuroendocrine tumors of the pancreas: A potential predictor of postoperative recurrence. Pancreatology. 2017;17:291–294.
23. Wong KK, Waterfield RT, Marzola MC, Scarsbrook AF, Chowdhury FU, Gross MD, Rubello D. Contemporary nuclear medicine imaging of neuroendocrine tumours. Clin Radiol. 2012;67:1035–1050.
24. Klimstra DS, Modlin IR, Coppola D, Lloyd R V., Suster S. The Pathologic Classification of Neuroendocrine Tumors. Pancreas. 2010;39:707–712.