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Jordan J Baechle, *Vanderbilt University*
Paula M Smith, *Vanderbilt University*
Marcus Tan, *Vanderbilt University*
Carmen C Solorzano, *Vanderbilt University*
Alexandra G Lopez-Aguiar, *Emory University*
Mary Dillhoff, *Ohio State University*
Eliza W Beal, *Ohio State University*
George Poultsides, *Stanford University*
Elefherios Makris, *Stanford University*
Flavio G Rocha, *Virginia Mason Medical Center*

Only first 10 authors above; see publication for full author list.

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Specific Growth Rate as a Predictor of Survival in Pancreatic Neuroendocrine Tumors: A Multi-institutional Study from the United States Neuroendocrine Study Group

Jordan J. Baechle, BS[1], **Paula Marincola Smith, MD**[1], **Marcus Tan, MD**[1], **Carmen C. Solórzano, MD**[1], **Alexandra G. Lopez-Aguiar, MD**[2], **Mary Dillhoff, MD**[3], **Eliza W. Beal, MD**[3], **George Poultsides, MD**[4], **Eleftherios Makris, MD**[4], **Flavio G. Rocha, MD**[5], **Angelena Crown, MD**[5], **Clifford Cho, MD**[6], **Megan Beems, MD**[6], **Emily R. Winslow, MD**[7], **Victoria R. Rendell, MD**[7], **Bradley A. Krasnick, MD**[8], **Ryan Fields, MD**[8], **Shishir K. Maithel, MD**[2], **Christina E. Bailey, MD**[1], **Kamran Idrees, MD**[1]

[1]Department of Surgery, Vanderbilt University Medical Center, Nashville, TN

[2]Department of Surgery, Winship Cancer Institute, Emory University, Atlanta, GA

[3]The Ohio State University Comprehensive Cancer Center, Columbus, OH

[4]Stanford University Medical Center, Stanford, CA

[5]Virginia Mason Medical Center, Seattle, WA

[6]Division of Hepatopancreatobiliary and Advanced Gastrointestinal Surgery, Department of Surgery, University of Michigan, Ann Arbor, MI

[7]School of Medicine and Public Health, University of Wisconsin, Madison, WI

[8]Washington University School of Medicine, St Louis, MO

Abstract

Background.—Pancreatic neuroendocrine tumors (PNETs) are often indolent; however, identifying patients at risk for rapidly progressing variants is critical, particularly for those with small tumors who may be candidates for expectant management. Specific growth rate (SGR) has been predictive of survival in other malignancies but has not been examined in PNETs.

Methods.—A retrospective cohort study of adult patients who underwent PNET resection from 2000 to 2016 was performed utilizing the multi-institutional United States Neuroendocrine Study Group database. Patients with ≥ 2 preoperative cross-sectional imaging studies at least 30 days apart were included in our analysis (N = 288). Patients were grouped as "high SGR" or "low SGR." Demographic and clinical factors were compared between the groups. Kaplan–Meier and log-rank analysis were used for survival analysis. Cox proportional hazard analysis was used to assess the impact of various clinical factors on overall survival (OS).

K. Idrees, MD kamran.idrees@vanderbilt.edu; kamran.idrees@vumc.org.

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Results.—High SGR was associated with higher *T* stage at resection, shorter doubling time, and elevated HbA1c (all $P \leq 0.01$). Patients with high SGR had significantly decreased 5-year OS (63 vs 80%, $P = 0.01$) and disease-specific survival (72 vs 91%, $P = 0.03$) compared to those with low SGR. In patients with small (≤ 2 cm) tumors ($N = 106$), high SGR predicted lower 5-year OS (79 vs 96%, $P = 0.01$). On multivariate analysis, high SGR was independently associated with worse OS (hazard ratio 2.67, 95% confidence interval 1.05–6.84, $P = 0.04$).

Conclusion.—High SGR is associated with worse survival in PNET patients. Evaluating PNET SGR may enhance clinical decision-making, particularly when weighing expectant management versus surgery in patients with small tumors.

Pancreatic neuroendocrine tumors (PNETs) are a rare gastrointestinal malignancy with an annual incidence of 2–3 per 100,000 in the United States (US).[1,2] While 10% of PNETs are associated with hormone-hypersecretion syndromes such as insulinomas, gastrinomas, VIPomas, and glucagonomas,[3] the majority are non-functional.[4] Though PNETs are often considered indolent relative to other gastrointestinal malignancies including pancreatic adenocarcinoma (with a 5-year overall survival (OS) of 74% vs 7%, respectively[5,6]), it is estimated that approximately 10% of PNETs exhibit aggressive behavior.[7–11] PNET related death is most often the result of metastasis to the liver.[12] Complete surgical resection remains the only curative treatment for PNETs,[13] and resection of both primary and metastatic tumors has been associated with improved OS.[14–16]

Though surgical resection is the mainstay of treatment, because of their relatively indolent nature, current treatment guidelines support expectant management of small, non-functional PNETs.[17–20] In fact, several treatment algorithms advocate observation with serial imaging of patients with non-functional PNETs ≤ 2 cm in size.[19,20] However, little research has been done to risk-stratify PNET patients to more accurately identify those at risk of rapidly progressive variants, and factors predictive of more aggressive tumor kinetics remain poorly understood. Identifying risk factors associated with more aggressive tumor biology could have a significant impact on the management and counseling of patients with newly diagnosed PNETs, particularly those with small, non-functional tumors who might otherwise be managed expectantly.

Dr. Mordecai Schwartz's growth rate formula (specific growth rate, SGR) utilizes sequential measurements to estimate cancerous tumor growth rate.[21,22] This equation's application to serial cross-sectional imaging studies and its translation to tumor volume doubling time are common non-invasive means of quantifying tumor growth rate.[22] It has been shown to be predictive of cancer-related survival in several malignancies including lung cancer,[23,24] gastric cancer,[25] pancreatic cancer,[26,27] hepatocellular carcinoma,[28] cholangiocarcinoma,[29] renal cell carcinoma,[30] melanoma,[31,32] and unresectable neuroendocrine tumors.[33] Despite its utility in predicting outcomes in a multitude of malignancies, the ability of SGR to predict tumor behavior or cancer-related survival has not been examined in resectable PNETs. The primary aim of this study was to evaluate SGR as a prognostic indicator in PNET patients who underwent primary surgical resection and to identify factors associated with elevated PNET SGR, utilizing a large multi-institutional retrospective database.

METHODS

Data Collection and Study Design

The US Neuroendocrine Tumor Study Group (US-NETSG) is a collaboration of eight academic medical centers: Vanderbilt University, Emory University, Stanford University, The John Hopkins University, The Ohio State University, Washington University in St. Louis, University of Michigan, and University of Wisconsin. Adult patients who underwent resection of gastrointestinal neuroendocrine tumors (stages I–IV) between 2000 and 2016 were retrospectively identified at each institution. Data collection was approved by the Institutional Review Boards at each participating institution.

Over 750 parameters were collected in the database for each patient, including but not limited to demographics, general health information and comorbidities, preoperative imaging and laboratory data, intraoperative data, pathology data, postoperative complications, and time to recurrence/progression/death. The American Joint Commission on Cancer Staging Manual, seventh edition, was used to define TNM classification. Survival data were determined by chart review and confirmed with the Social Security Death Index database. The de-identified data from each institution was shared amongst the collaborating institutions for analysis.

All patients with 2 or more preoperative cross-sectional imaging studies at least 30 days apart were included in our analysis. The tumor SGR (% growth/day, %/d)[21,22] was calculated utilizing the previously published formula (below); the tumor diameter was measured on initial (D_i) and final (D_f) preoperative imaging, where $T - T_o$ is the time in days between initial and final preoperative imaging studies.

$$\mathrm{SGR} = 3 \times \ln\left(\frac{D_i}{D_f}\right)/(T - T_o).$$

Statistical Analysis

Previous studies have suggested that 10% of PNETs exhibit more aggressive tumor biology and kinetics.[3] As such, the 90th percentile of SGR in our patient cohort was identified by density plot (Fig. 1) and those patients with an SGR greater than the 90th percentile were termed “high SGR” while the remaining patients were termed “low SGR“. Demographic, preoperative, intraoperative, pathologic, and survival data were compared between high and low SGR groups as well as between patients in our study cohort compared to the PNET patients in the entirety of the US-NETSG database. Categorical variables were presented as frequency and percentages and compared using Chi square or Fisher’s exact test, as appropriate. Continuous variables were reported as median value with interquartile range (IQR) unless otherwise specified and compared using the Kruskal–Wallis test. Overall survival (OS) and disease-specific survival (DSS) were calculated using the Kaplan–Meier method and compared using the log-rank test. A sub-analysis of patients (stage I–IV) with small (≤ 2 cm) tumors was additionally performed. Clinical and pathological data were analyzed using multivariate Cox regression and adjusted odds ratio (AOR). Significance was

set at a *P* value lower than 0.05. All statistical analysis was performed using 1.1.383 R statistics software (R Core Team Vienna, Austria).

RESULTS

Of the 2022 patients who underwent neuroendocrine tumor resection during the study period (2000–2016) at any of the US-NETSG participating institutions, 1247 (62%) had PNETs. Of these 1247 patients with PNETs, 288 (23%) had two or more preoperative cross-sectional imaging studies at least 30 days apart and thus met the criteria for growth rate calculation and inclusion in our analysis.[22] The median SGR for all PNETs studied was 0.02%/d (IQR 0.00–0.30%/d). The 90th percentile of SGR was 0.93%/d (Fig. 1). Those with SGRs greater than or equal to 0.93%/d were categorized as "high SGR" ($N = 29$) and the rest categorized as "low SGR" ($N = 259$). The median time between imaging studies was 144 days for all patients.

Patient demographic, preoperative, and pathologic characteristics by SGR group is summarized in Table 1. Within the study cohort, high and low SGR groups were similar in age, gender, race, BMI, insurance status, functional status, and ASA class. The groups had similar median tumor size at the time of resection (2.50 cm for low SGR group and 2.95 cm for high SGR group; $P = 0.858$). Compared to the low SGR group, the high SGR group had significantly higher *T* Stage at initial resection ($P = 0.011$), shorter doubling time ($P < 0.001$), and higher hemoglobin A1c (HbA1c, $P = 0.012$). A table comparing demographic and pathological factors of our study cohort compared to PNET patients in the entirety of the US-NETSG database is provided in Supplemental Table 1.

Elevated HbA1c (≥ 6.5%) was significantly associated with increased SGR when compared with normal HbA1c (< 6.5%) ($P = 0.039$) (Fig. 2). Additionally, when controlling for insulin use and obesity (BMI ≥ 30), elevated HbA1c was significantly and independently associated with elevated SGR [AOR 15.01, 95% confidence interval (CI) 2.02–158, $P = 0.012$] (Supplemental Table 2).

The 1-, 5-, and 10-year survival rates were 97.1%, 80.2%, and 62.4%, respectively, for patients with a low SGR, and 84.3%, 63.1%, and 0% for those with high SGR ($P = 0.013$). The high SGR group had significantly shorter OS (median OS 79.8 months vs not reached, $P = 0.013$) and DSS (median DSS 120 months vs not reached, $P = 0.025$) compared to the low SGR group (Fig. 3a, b). Additionally, on sub-analysis of the 106 patients of all stages with small (≤ 2 cm) PNETs, those patients with small tumors and a high SGR had significantly shorter OS compared to those with small tumors and low SGR (median OS not reached for either group, $P = 0.007$, Fig. 3c).

On multivariate Cox regression analysis, high SGR [hazard ratio (HR) 2.67; 95% CI 1.05–6.84, $P = 0.040$], *T* stage ≥ 3 (HR 3.14, 95% CI 1.07–7.87, $P = 0.038$), and presence of metastatic disease at index operation (HR 2.11, 95% CI 1.05–4.25, $P = 0.036$) were independently associated with worse OS (Table 2).

DISCUSSION

In the current study, we observed a significant correlation between elevated preoperative SGR and worse OS and DSS following surgical resection of PNETs. Previous studies have identified preoperative PNET size as a predictor of outcomes with tumors > 2 cm considered to be high risk for malignant potential.[17–19] To date, emphasis on this 2-cm size threshold and fine needle aspiration cytology have served as primary surrogates for estimating tumor aggression preoperatively, and it's these factors that play a decisive role in algorithms and protocols guiding management of PNETs.[3,18–20] Our study suggests that quantifying PNET SGR preoperatively may be a helpful supplement to the clinical management of PNETs as an additional indicator of tumor growth kinetics and predictor of overall survival, particularly in the setting of small tumors that are often surveilled with serial imaging.

Even for PNET patients whose tumors remained small (≤ 2 cm) on final preoperative imaging, we found that high SGR is a significantly associated with worse OS. This suggests that even for patients with small PNETs who are generally felt to be safely followed with expectant management,[18,19] there is a subset with more rapidly growing tumors who have worse outcomes. Though this retrospective analysis is not designed to directly compare the management strategies in patients with low and high SGR, this finding suggests that patients with small tumors who are being followed with serial imaging who demonstrate high SGR might benefit from earlier surgical resection, even if their tumor remains at or below the traditional size threshold of 2 cm.

Additionally, our study demonstrated a significant and independent association between poor glycemic control, as indicated by elevated (≥ 6.5%) preoperative HbA1c level, and high SGR, when controlling for insulin use and obesity. Though a mechanism ascribing causation to such an association is not fully understood, we believe this to be a compelling finding considering recent literature that suggests a causal mechanism between elevated HbA1c and elevated SGR[34–37] as well as a correlation between increased tumor volume and impaired glycemic control.[7] In the US, 55.2% of patients with PNETs either have a pre-existing diagnosis of diabetes mellitus (DM) or are newly discovered to have DM at the time of their PNET diagnosis.[38] Further studies, however, are required to determine definitively whether a causative relationship exists between poor glycemic control and elevated SGR in PNET patients.[39–41]

We acknowledge this study carries several limitations. First, inherent biases exist in any retrospective study and limits our ability to make conclusions about causality. Second, because our retrospective database includes only those patients who underwent PNET resection, we fail to capture those patients being treated non-operatively (including those with small tumors who are being observed or those with unresectable disease) which would enable us to gain more understanding of the impact of SGR and HbA1c in other subsets of PNET patients. Third, though the multi-institutional nature of this study allowed us to assemble a sufficiently robust database to analyze the natural course of this rare tumor, the collaboration was limited to large, academic referral centers which may lead to selection bias and limit the generalizability of our conclusions.

Additionally, the US-NETSG database is somewhat limited on data related to tumor biology, including data on tumor grade, Ki-67, mitotic index, and differentiation, and we therefore were unable to fully examine these factors as they relate to SGR in our patient cohort. Furthermore, due to the multi-institutional nature of our collaborative effort, the possibility of variability in imaging, data collection, and reporting protocols between the eight institutions certainly exists. As with many collaborative databases, the US-NETSG has missing data which unfortunately left the study under-powered to perform a multivariable analysis of disease-specific survival.

Moreover, although tumor SGR has been shown to vary over the course of time, and across primary and metastatic tumors, our analysis was limited to two primary tumor measurements only and therefore assumes a constant SGR, which may not be wholly representative of irregularities in growth pattern and does not take into consideration the SGR of metastatic lesions. Though some argue that SGR can mislead physicians and patients to under-appreciate the degree of continuously compounding growth compared to other means of reporting tumor proliferation (such as doubling time), we chose to utilize SGR due to its precision in calculating low growth rates[22] which is critical when analyzing the behavior of these relatively indolent tumors. Such small changes in tumor volume, common in slow growing tumors such as PNETs, calculate infinite and even undefined doubling times, which are meaningless clinically. On the other hand, the degree of SGR uncertainty increases with a shorter time interval between tumor measurements. Our exclusion criteria aimed to mitigate this limitation by using only imaging studies that were at least 30 days apart, which has been shown to be associated with improved SGR accuracy and reproducibility.[22] Lastly, we acknowledge that cross-sectional diameter measurements assume spherical tumor shape and do not always translate to true changes in volume of irregularly shaped tumors.

Despite these limitations, our database was large enough to capture and quantify the rapidly progressing PNET variants observed and reported in previous studies.[10,11] We demonstrated that elevated HbA1c was independently associated with high tumor SGR and that high SGR appears to be a predictor of worse overall and disease-specific survival in PNET patients, as has been demonstrated in several other malignancies.[22–31] Additionally, due in part to the increased use of cross-sectional imaging and rate of incidental diagnoses, the incidence of non-functional PNETs ≤ 2 cm has increased sevenfold over the past 22 years in the United States.[42] For these patients who do have small, asymptomatic, and nonfunctional tumors who are being followed non-operatively, our data suggest that SGR calculation may be beneficial to further refine the treatment algorithm of expectant management versus early surgical resection. Lastly, we found that, when controlling for preoperative insulin use and obesity, elevated preoperative HbA1c level was independently associated with high SGR in PNET patients, suggesting that HbA1c may be useful preoperatively to identify those at risk of aggressive tumor behavior.

In conclusion, elevated SGR, which has been used as a prognostic indicator in other malignancies, appears to be significantly associated with worse survival in patients with surgically resected PNETs. The findings of this retrospective study would benefit from validation in a prospective manner, though we acknowledge conducting such prospective

analyses can be challenging in the setting of rare tumors such as PNETs. Consideration of repeat surveillance of cross-sectional imaging as early as 30 days following initial imaging and using this data to calculate SGR in patients with small (≤ 2 cm) tumors who are already being observed with serial imaging under current treatment guidelines may be beneficial. For those with elevated SGR (even if their tumor remains small), one might consider surgical resection rather than continued observation or at the minimum more frequent imaging. Additionally, HbA1c may be a useful predictor of high SGR and one could consider routine preoperative HbA1c measurement in those PNET patients with DM diagnoses or those with DM risk factors. Further prospective trials would be beneficial in determining whether improved glycemic control has the potential to alter SGR and oncologic outcomes in PNET patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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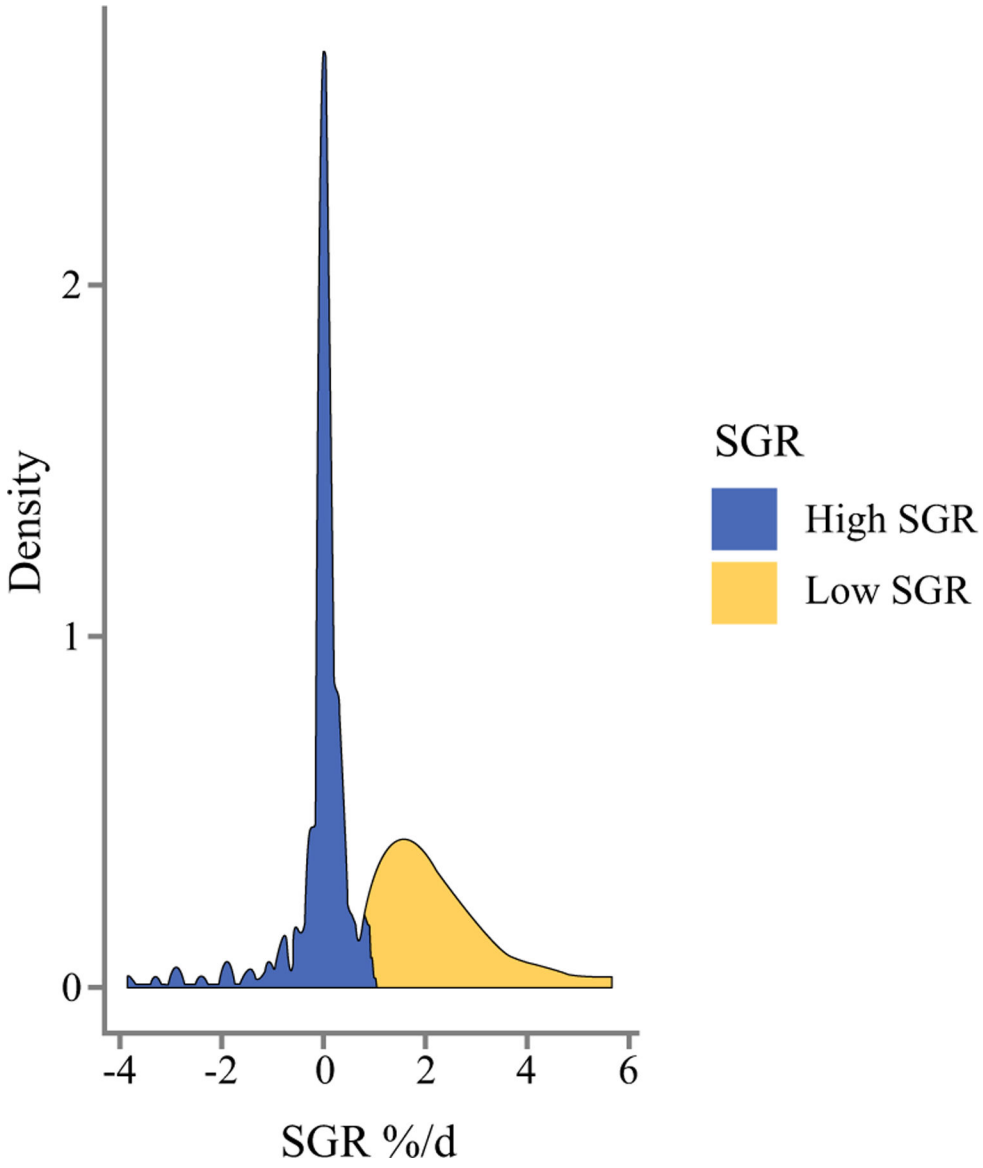

FIG. 1.

Density plot for the specific growth rate of PNET patients, stratified to identify the 90th percentile

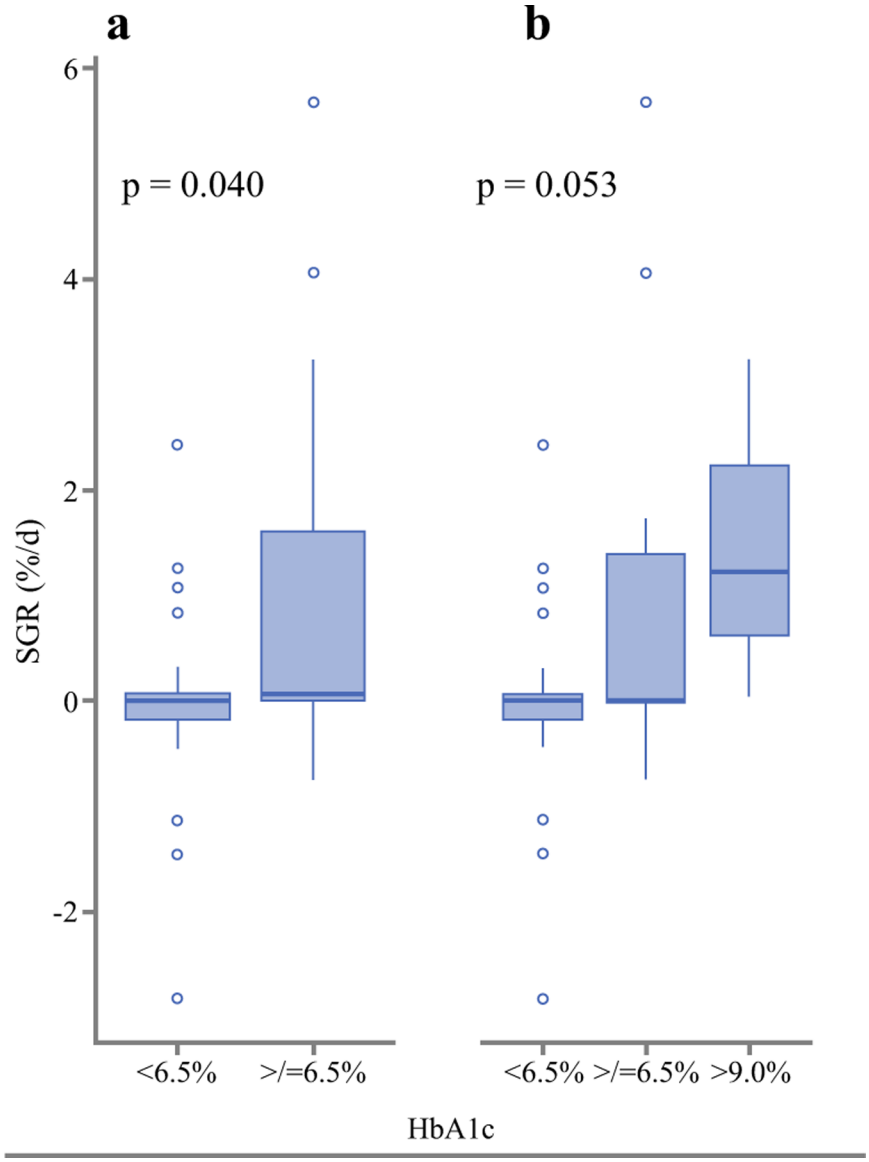

FIG. 2.

Box plot comparing SGR of PNET patients according to **a** HbA1c% < 6.5% vs ≥ 6.5%, and **b** < 6.5% versus 6.5–9.0% vs > 9.0%

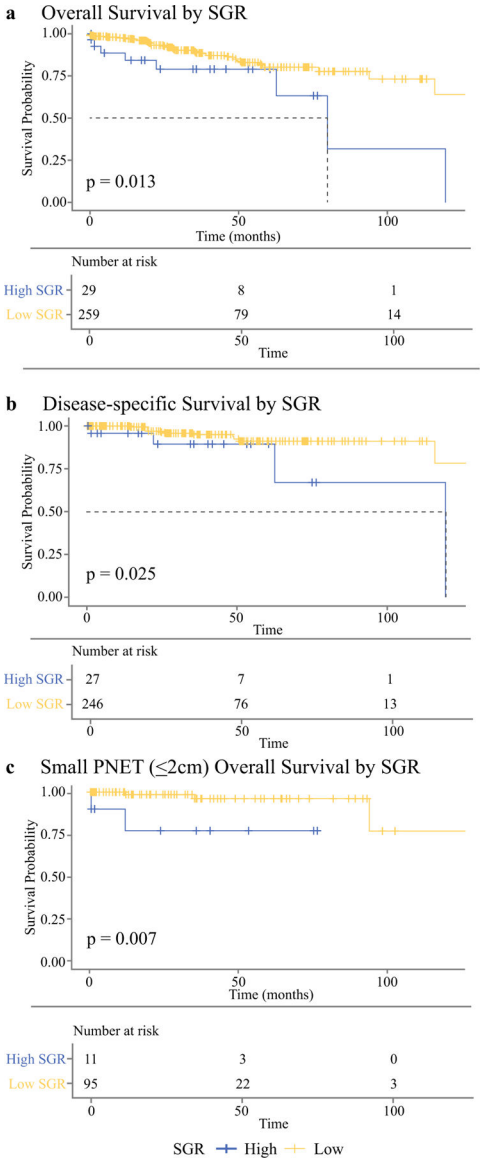

FIG. 3.

PNET Kaplan–Meier survival analysis. **a** Overall survival by SGR, **b** disease-specific survival by SGR, **c** small PNET (≤ 2 cm) overall survival by SGR

Ann Surg Oncol. Author manuscript; available in PMC 2023 May 13.

TABLE 1

Demographics, pre-operative factors, and pathologic features by SGR

Variable	Low SGR, *N* (%)	High SGR, *N* (%)	*P* value
Total	259	29	
SGR (%/day)—(IQR)	0.00 [− 0.05;0.20]	1.82 [1.34;2.75]	< **0.001**
Doubling time[a] (days)—(IQR)	293 [179;628]	38.0 [25.2;51.8]	< **0.001**
Demographics and pre-operative factors			
Gender			
Male	141 (54.4)	17 (58.6)	0.816
Female	118 (45.6)	12 (41.4)	
BMI—(IQR)	27.4 [24.0;31.2]	27.5 [25.3;33.7]	0.516
Age—(IQR)	57.5 [48.0;66.8]	58.5 [45.6;65.1]	0.981
Insurance status			
Priv. insured	165 (63.7)	21 (72.4)	0.383
Gov. insured	79 (30.5)	6 (20.7)	
Uninsured	8 (3.1)	2 (6.9)	
Unknown	7 (2.7)	0 (0.0)	
Race			
White	183 (70.7)	20 (69.0)	0.605
Black	26 (10.0)	3 (10.3)	
Other	50 (19.3)	6 (20.7)	
Functional status			
Independent	215 (92.3)	28 (96.6)	0.705
Dependent[b]	18 (7.7)	1 (3.5)	
HTN			
Yes	126 (49.2)	12 (41.4)	0.545
No	130 (50.8)	17 (58.6)	
ASA class			
I	5 (1.9)	1 (3.5)	0.793
II	76 (29.3)	9 (31.0)	

Variable	Low SGR, *N* (%)	High SGR, *N* (%)	*P* value
III	162 (62.5)	17 (58.6)	
IV	7 (2.7)	1 (3.5)	
Unknown	9 (3.5)	1 (3.5)	
ECOG			
0	170 (65.6)	20 (69.0)	0.765
1	26 (10.0)	3 (10.3)	
2	4 (1.5)	1 (3.5)	
3	2 (0.8)	0 (0.0)	
Unknown	57 (22.0)	5 (17.2)	
Pre-op diabetes status			
No DM Dx	193 (74.5)	21 (72.4)	0.882
DM—no meds	4 (1.5)	0 (0.0)	
DM—oral meds	32 (12.4)	4 (13.8)	
DM—insulin	27 (10.4)	4 (13.8)	
Unknown	27 (10.4)	0 (0.0)	
Intent			
Curative	229 (88.4)	25 (86.2)	0.760
Noncurative	30 (11.6)	4 (13.8)	
Pathologic features			
Tumor size[C]—(IQR)	2.50 [1.50;4.00]	2.95 [1.52;4.48]	0.858
Ki-67 index—(IQR) (*n* = 140)	3.00 [2.00;5.00]	5.00 [2.00;10.5]	0.083
HbA1c %—(IQR) (*n* = 49)	5.65 [5.30;6.18]	6.90 [6.00;7.90]	**0.012**
T stage			
*T*1	94 (36.3)	10 (34.5)	**0.011**
*T*2	83 (32.0)	4 (13.8)	
*T*3	73 (28.2)	10 (34.5)	
*T*4	1 (0.4)	1 (3.5)	
Tx	8 (3.1)	4 (13.8)	
N stage			
*N*0	150 (57.9)	15 (51.7)	0.203
*N*1	78 (30.1)	7 (24.1)	

Variable	Low SGR, *N* (%)	High SGR, *N* (%)	*P* value
Nx	31 (12.0)	7 (24.1)	
M stage			
*M*0	209 (80.7)	20 (69.0)	0.066
*M*1	43 (16.6)	6 (20.7)	
Mx	7 (2.7)	3 (10.3)	
Grade			
Well diff.	219 (84.6)	23 (79.3)	0.332
Moderately diff.	12 (4.6)	1 (3.5)	
Poorly diff.	5 (1.9)	2 (6.9)	
Unknown	23 (8.9)	3 (10.3)	
Histology type			
NET	205 (79.2)	21 (72.4)	0.127
NEC	37 (14.3)	3 (10.3)	
Other	17 (6.6)	5 (17.2)	
PNET location			
Head	82 (31.7)	7 (24.1)	**0.022**
Uncinate	20 (7.7)	0 (0.0)	
Neck	15 (5.8)	1 (3.5)	
Body	47 (18.1)	11 (37.9)	
Tail	89 (34.4)	7 (24.1)	
Unknown	6 (2.3)	3 (10.3)	
Tumor function			
Nonfunctional	229 (88.4)	27 (93.1)	1.00
Insulinoma	16 (6.2)	1 (3.5)	
Other	14 (5.4)	1 (3.5)	
LVI			
Yes	76 (29.3)	14 (48.3)	0.094
No	157 (60.6)	12 (41.4)	
Unknown	26 (10.0)	3 (10.3)	
PNI			
Yes	46 (17.8)	8 (27.6)	0.321

Ann Surg Oncol. Author manuscript; available in PMC 2023 May 13.

Variable	Low SGR, *N* (%)	High SGR, *N* (%)	*P* value
No	173 (66.8)	16 (55.2)	
Unknown	40 (15.4)	5 (17.2)	
Margin status			
Positive	37 (14.3)	5 (17.2)	0.057
Negative	216 (83.4)	21 (72.4)	
Unknown	6 (2.3)	3 (10.3)	

$P < 0.05$ values are given in bold

IQR interquartile range, *Priv.* private, *Gov.* government, *HTN* hypertension, *ASA class* American Society of Anesthiologists Physical Status Classification System, *ECOG performance status* Eastern Cooperative Oncology Group Score, *Dx* diagnosis, *DM* diabetes mellitus, *HbA1c* hemoglobin A1c, *T* tumor, *N* nodes, *M* metastasis, *Tx*, *Mx*, and *Nx* undefined staging data, *Diff.* differentiation, *NET* neuroendocrine tumor, *NEC* neuroendocrine carcinoma, *LVI* lymphovascular invasion, *PNI* perineural invasion

[a] Doubling time limited to defined and positive values

[b] Partially or totally dependent

[c] Tumor size on resection

Ann Surg Oncol. Author manuscript; available in PMC 2023 May 13.

TABLE 2

Cox multivariate regression analysis for overall survival

Variable	HR	95% CI	*P* value
High SGR	**2.67**	**1.05–6.84**	**0.040**
T stage			
*T*2	2.64	0.88–7.87	0.083
≥ *T*3	3.14	1.07–9.26	0.038
N stage			
*N*1	0.73	0.36–1.44	0.361
M stage			
*M*1	2.11	1.05–4.25	0.036
HbA1c ≥ 6.5%	3.45	0.80–14.89	0.096

P < 0.05 values are given in bold