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Authors

Gratian, Lauren
Pura, John
Dinan, Michaela
et al.

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Impact of Extent of Surgery on Survival in Patients with Small Nonfunctional Pancreatic Neuroendocrine Tumors in the United States

Lauren Gratian, MD[1], **John Pura, MPH**[2], **Michaela Dinan, PhD**[3], **Sanziana Roman, MD**[4], **Shelby Reed, PhD**[3], and **Julie Ann Sosa, MD**[3,4]

Sanziana Roman: sanziana.roman@duke.edu

[1]Division of Endocrinology Department of Medicine, Duke University School of Medicine, Durham, NC

[2]Department of Biostatistics, Duke University School of Medicine, Durham, NC

[3]Duke Clinical Research Institute, Durham, NC

[4]Section of Endocrine Surgery, Department of Surgery, Duke University School of Medicine, Durham, NC

Abstract

Background—Nonfunctional pancreatic neuroendocrine tumors (PNETs) ≤2 cm have uncertain malignant potential, and optimal treatment remains unclear. Objectives of this study were to better understand their malignant potential, determine whether extent of surgery or lymph node dissection is associated with overall survival (OS), and identify other factors associated with OS.

Methods—Patients with nonfunctional PNETs ≤2 cm were identified from the National Cancer Data Base (1998 to 2011). Descriptive statistics were used for patient characteristics and surgical resection patterns. Five-year OS was estimated using Kaplan–Meier analyses across extent of surgery and compared using the log-rank test. Cox proportional regression modeling was used to test the association between survival and extent of surgery.

Results—A total of 1854 patients with nonfunctional PNETs ≤2 cm were included. From 1998 to 2011, these tumors increased three-fold as a proportion of all PNETs. Among tumors ≤0.5 cm, 33 % presented with regional lymph node metastases and 11 % with distant metastases. Five-year OS for patients not undergoing surgery was 27.6 % vs. 83.0 % for partial pancreatectomy, 72.3 % for pancreaticoduodenectomy, and 86.0 % for total pancreatectomy ($p < 0.01$). Multivariate analysis demonstrated no difference in OS based on type of surgery or the addition of regional lymphadenectomy ($p = 0.16$). Younger age and later year of diagnosis were independently associated with improved survival.

Conclusions—Small nonfunctional PNETs represent an increasing proportion of all PNETs and have a significant risk of malignancy. Survival is improving over time despite older age at

Disclosure: The authors declare no conflict of interest. The data used in the study are derived from a deidentified 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 used, or the conclusions drawn from these data by the investigators.

diagnosis. Type of surgical resection and the addition of lymph node resection were not associated with OS.

Pancreatic neuroendocrine tumors (PNETs) account for 1 % of all pancreatic neoplasms, but their incidence is increasing.[1] An examination of the Surveillance Epidemiology and End Results database demonstrated a three-fold increase in incidence from 1973 to 2007, a large proportion of which may be attributed to tumors ≤2 cm.[2, 3] The rising incidence of smaller PNETs is important because these tumors have uncertain malignant potential, and optimal surgical intervention remains unclear.

The benefit of surgical resection for nonfunctional PNETs ≤2 cm remains controversial.[4–6] According to National Comprehensive Cancer Network guidelines, patients with nonfunctional PNETs <2 cm are considered candidates for enucleation, pancreaticoduodenectomy, or spleen-preserving distal pancreatectomy. Observation alone is an option for select tumors <1 cm that are incidentally discovered.[7] However, current European Neuroendocrine Tumor Society (ENETS) guidelines state, "No data exist with respect to a positive effect of surgery on overall survival (OS) in small (<2 cm), possibly benign or intermediate-risk pancreatic endocrine tumors." [8] Experts agree that malignant-appearing lesions should be resected. However, preoperative risk assessment for these tumors is challenging. According to the World Health Organization classification system, PNETs can be considered benign if they are <2 cm, confined to the pancreas, nonangioinvasive, with ≤2 mitosis/HPF and ≤2 % Ki67-positive cells.[9] This classification system requires surgical pathology, which is rarely available in the preoperative planning stages. Furthermore, there is mounting evidence documenting the presence of nodal and distant metastasis and recurrence in tumors that meet preoperative criteria for benign disease (i.e., intrapancreatic tumors <2 cm).[3, 5, 6, 10]

The prognostic value of lymph node resection also remains unclear. There are currently two staging systems for PNETs that incorporate lymph node status (ENETS and the American Joint Committee on Cancer).[11–13] Both staging systems are highly prognostic for relapse-free survival and OS.[14–16] However, several population-level studies have failed to demonstrate lymph node status as an independent predictor of disease-specific survival.[3, 17]

In this study, we examined the proportion of all nonfunctional PNETs ≤2 cm from 1998 through 2011, the malignant potential of these tumors, and whether type of surgery, lymph node dissection, or other factors were associated with OS.

Methods

Data Source and Patient Selection

The National Cancer Data Base (NCDB) is a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. It was established in 1989 as a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set. This database captures 70 % of all newly diagnosed malignancies in the United States.[18]

Using the NCDB (1998 to 2011), patients were identified on the basis of International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), for tumors of the pancreas: C25.0 to C25.9. Histology ICD-O-3 codes were used to select patients with nonfunctional PNETs (islet cell 8150; neuroendocrine tumors not otherwise specified 8246). We excluded patients with unknown surgical status or nonspecific surgical type (surgery or pancreatectomy not otherwise specified) and those with more than one malignant primary tumor. For the survival analysis, we limited cases to those with time between diagnosis and death greater than 0 months and cases diagnosed in 2006 or earlier to ensure that there were at least 5 years of follow-up. Surgical groups were defined as no surgery, partial pancreatectomy including enucleation, pancreaticoduodenectomy with or without partial gastrectomy, and total pancreatectomy with or without partial gastrectomy or duodenectomy. Lymph nodes were considered examined if they were surgically removed or aspirated and considered positive if malignant cells were identified. Distant metastases were based on American Joint Committee on Cancer clinical staging. Surgical margins were considered positive if there was evidence of microscopic or macroscopic residual tumor. We examined length of stay (LOS), unplanned 30-day readmission rates, and OS. This study was determined by the institutional review board to be exempt as a result of the deidentified nature of the data.

Statistical Analysis

Baseline characteristics were reported using medians with 25th and 75th percentiles for continuous variables and proportions for categorical variables. Descriptive data were compared across groups using the Kruskal–Wallis test and Pearson Chi square or Fisher's exact tests. OS was defined from the time of diagnosis to death or last follow-up. Survival time was censored for patients alive at the end of the study period. Estimates and 95 % confidence intervals of OS proportions were computed using the Kaplan–Meier method, and survival distributions were compared across groups using the log-rank test.

A marginal Cox proportional hazard regression model was constructed to evaluate the association between survival time and extent of surgery, adjusting for covariates and accounting for clustering within facility centers. Continuous covariates in the model included patient age, year of diagnosis, tumor size, and hospital case volume. Hospital volume was calculated as the total number of cases within a facility for a given year. Categorical covariates included facility type, patient gender and race, surgery type, surgical site, administration of chemotherapy or radiation, comorbidities, and margin status. Missing values for categorical variables were multiply imputed using chained equations.[19] Twenty imputed data sets were created using SAS-callable Imputation and Variance Estimation Software (IVEware, University of Michigan). Tabulations of missing variables confirmed similar proportions across imputed data sets.

To determine risk factors associated with OS, a backward selection for the marginal Cox proportional hazard regression model above was performed. Variables with a p value of <0.2 remained in the model. Risk factors selected in at least 15 of 20 data sets were considered for the final model. Secondary analyses describing 30-day readmission and LOS across extent of surgery were addressed using Pearson Chi square and Kruskal–Wallis tests,

respectively. Analyses were performed by SAS version 9.3 statistical software (SAS Institute, Cary, NC).

Results

A total of 1,854 adult patients with nonfunctional PNETs ≤2 cm were identified. After excluding patients with unknown surgical status or nonspecific surgical type, the study cohort included 1,367 cases (Table 1). Survival analysis was further limited to 366 patients (Fig. 1).

Proportion of all PNETs

In 1998, there were 40 cases of small nonfunctional PNETs reported, which made up 7 % of all PNETs (581) reported that year. In 2011, there were 351 cases of small nonfunctional PNETs reported, which made up 20 % of all PNET cases (1,716).

Malignant Potential

Overall, 303 patients (29 %) presented with regional lymph node metastases, and 180 patients (10 %) presented with distant metastases. There was no association between decreasing tumor size and decreased percentage of cases presenting with regional nodal metastasis. However, larger size was positively associated with presence of distant metastasis (14.2 % in size >1 to ≤2 cm, 8.5 % in size >0.5 to ≤1 cm, and 10.5 % in size ≤0.5 cm) (Fig. 2). There was no change in the proportion of patients who presented with distant metastases over time.

Surgical Resection of Primary Tumor

Forty-three percent of patients underwent partial pancreatectomy, 24 % pancreaticoduodenectomy, and 7 % total pancreatectomy. Patient age, gender, race, and comorbidities were similar across surgery types. Positive margins were reported in more patients who underwent partial pancreatectomy compared to pancreaticoduodenetomy or total pancreatectomy. Thirteen percent of patients who underwent total pancreatectomy experienced an unplanned readmission compared to 9 % of patients who underwent partial pancreatectomy or pancreaticoduodenectomy ($p = 0.53$). LOS was longer for pancreaticoduodenectomy, with a median of 8 days compared to 6 days for partial pancreatectomy and 6 days for total pancreatectomy ($p < 0.01$). A total of 73 deaths were observed over a median follow-up of 5.2 years. Unadjusted 5-year OS for partial pancreatectomy was 82.3 % (95 % confidence interval [CI] 73.4–88.5) compared to 72.3 % (95 % CI 60.4–81.2) for pancreaticoduodenectomy and 86 % (95 % CI 66.8–94.5) for total pancreatectomy (Fig. 3). After adjusting for age, race, comorbidities, location of tumor in pancreas, facility type, and treatment with chemotherapy or radiotherapy, there was no difference in risk of death across surgery types.

Lymphadenectomy

Among 999 patients who underwent surgical resection, 72.8 % had a lymphadenectomy. A median of eight lymph nodes were examined. Patients who underwent partial pancreatectomy were less likely to have regional lymph nodes examined compared to

patients who underwent pancreaticoduodenectomy or total pancreatectomy (63 vs. 89 % and 75 %, respectively). These patients were also less likely to have positive regional lymph nodes identified compared to patients who underwent pancreaticoduodenectomy or total pancreatectomy (13.4 vs. 30.6 % and 30.3 %, respectively). There was no difference in 2-year or 5-year OS in patients undergoing surgical resection between those who underwent lymphadenectomy and those who did not.

No Surgery

Twenty-seven percent of patients did not undergo surgery. Compared to patients who underwent resection, patients who did not undergo surgery were significantly older, more likely to have distant metastases and poorly differentiated grade tumors, and less likely to be treated in an academic center (Table 1). After excluding patients with distant metastases and those who were not offered surgery because it was contraindicated as a result of patient risk factors or did not undergo surgery because the patient died before surgery could be performed, unadjusted 5-year OS for patients not undergoing surgery was 27.6 % (95 % CI 16.9–39.4) compared to 83.0 % (95 % CI 74.0–89.1) for partial pancreatectomy, 72.3 % (95 % CI 60.4–81.2) for pancreaticoduodenectomy, and 86.0 % (95 % CI 66.8–94.5) for total pancreatectomy ($p < 0.01$).

Factors Associated with Survival

Older age at diagnosis was associated with reduced survival (hazard ratio [HR] 1.04 per year). Later year of diagnosis was associated with improved survival. Each later year of diagnosis from 1998 to 2006 was associated with an additional 15 % relative reduction in the risk of death (HR 0.85) (Fig. 4). To determine whether differential duration of follow-up impacted our findings, we censored patients diagnosed from 1998 to 2000 at 5 years and found similar results. We also examined the association between survival and year of diagnosis as a categorical variable using the Kaplan–Meier method. The risk of death for the years 2001 to 2003 was significantly lower than that of the 1998 to 2000 group (HR 0.21, 95 % CI 0.06–0.76, $p = 0.02$), but the risk of death for 2004–2006 was only marginally lower than that of 1998–2000 (HR 0.31, 95 % CI 0.09–1.13, $p = 0.08$). There were no differences in the proportions of patients treated with surgical resection, proportions presenting with distant metastases, or proportions treated at academic centers over time. There were trends toward older age at diagnosis and decreased proportions of patients with positive surgical margins over time.

Discussion

Between 1998 and 2011, nonfunctional PNETs ≤2 cm increased three-fold as a proportion of all PNETs. It is unclear whether this represents a true increase in incidence or an increase in diagnosis with the implementation of improved imaging. Medical providers encounter these small tumors more frequently and are tasked with determining treatment strategies in the face of uncertain malignant potential. We found that 29 % of these tumors presented with regional lymph node metastases. This estimate is higher than the 12–15 % previously demonstrated by Watzka et al. in an analysis that included both functional and nonfunctional

PNETs ≤2 cm.[10] We also found that a substantial proportion of these tumors presented with distant metastases, including 11 % of tumors ≤5 mm.

The addition of regional lymphadenectomy to surgical resection was not associated with OS. This finding is consistent with previous population-level studies.[3, 17] It has been postulated that this may be due to inadequate lymph node sampling. Parekh et al. conducted a retrospective review of 149 patients who underwent resection of PNETs at one institution during 1988 to 2010. Among patients who had lymphadenectomy, a median of only five lymph nodes were examined.[20] In our study, 27 % of patients who underwent surgery had no lymph nodes examined, and patients who underwent partial pancreatectomy were even less likely to have lymph nodes examined. Among patients who did have lymphadenectomy, a median of eight nodes were examined. It remains to be seen whether more extensive lymph node sampling predicts survival.

We found a significant reduction in OS in patients who did not undergo surgical resection compared to those who did. To our knowledge, this is the first study to demonstrate that surgical resection is associated with improved survival. Hill et al. demonstrated that surgical resection was associated with improved survival for patients with localized, regional, or metastatic PNETs.[21] However, they did not examine the subset of patients with nonfunctional tumors ≤2 cm. The benefit of surgery in this population is controversial. A retrospective cohort study of 133 patients treated at the Mayo Clinic concluded that incidentally discovered, nonfunctional PNETs <2 cm can be safely managed nonoperatively.[4] However, two separate institutional studies demonstrated disease-specific death in several patients with incidentally discovered nonfunctional PNETs ≤2 cm.[5, 6] Our finding of reduced survival in the no-surgery group should be interpreted with caution because these patients may not have been offered surgery as a result of unreported factors that increased their mortality. We attempted to control for these factors by excluding patients from the survival analysis if they had more than one primary malignancy, distant metastases, were not offered surgery as a result of comorbidities, or did not undergo surgery because they died before the recommended surgery. Prospective studies are needed to clarify this finding.

Multivariable analysis demonstrated that later year of diagnosis was associated with decreased risk of death. There was a 15 % reduction in the risk of death per year from 1998 through 2006 despite increasing patient age over time and no change in proportion of surgical resections, hospital type, or rate of distant metastasis. The difference between the results of the Cox proportional hazard model and the Kaplan–Meier method may be due to the higher granularity offered by the former model, which increases the power to detect an effect. In addition, the Cox model has the advantage of adjusting for the effects of other variables.

There are several limitations inherent to the NCDB database. The NCDB only collects data on tumors with ICD 0 to 3 codes corresponding to “malignant” disease. Therefore, these data may overestimate the malignant potential of these tumors. There is no explicit way to determine the functionality of a tumor. Nonfunctional PNETs are typically reported as neuroendocrine carcinomas or islet cell tumors. However, it is possible that some functional

tumors were inadvertently included in this study. We suspect the patients who underwent total pancreatectomy had multifocal disease. Multifocality is not reported in the database. Given this limitation, we analyzed these patients as a separate surgical group. Finally, our study was limited by potential coding errors, missing data, and the absence of several variables in the database, including mitotic rates, Ki67, disease-specific survival, and disease recurrence.

To our knowledge, this is the first study to examine nonfunctional PNETs ≤2 cm on a population level. Overall, our study confirms the relative increase in nonfunctional PNETs ≤2 cm as a function of all PNETs in the United States and demonstrates that small, nonfunctional PNETs have malignant potential. Survival is improving over time despite older age at diagnosis and no change in surgical resection, treatment facility type, or proportion of cases with distant metastases. Extent of surgical resection and the addition of lymph node resection were not associated with OS.

Nonfunctional PNETs of all sizes should be considered potentially malignant, and surgical resection should be considered. Type of surgical resection does not appear to affect OS and can be determined at the discretion of the surgeon. Prospective studies are needed to clarify the potential benefits of surgery on survival for nonfunctional PNETs ≤2 cm.

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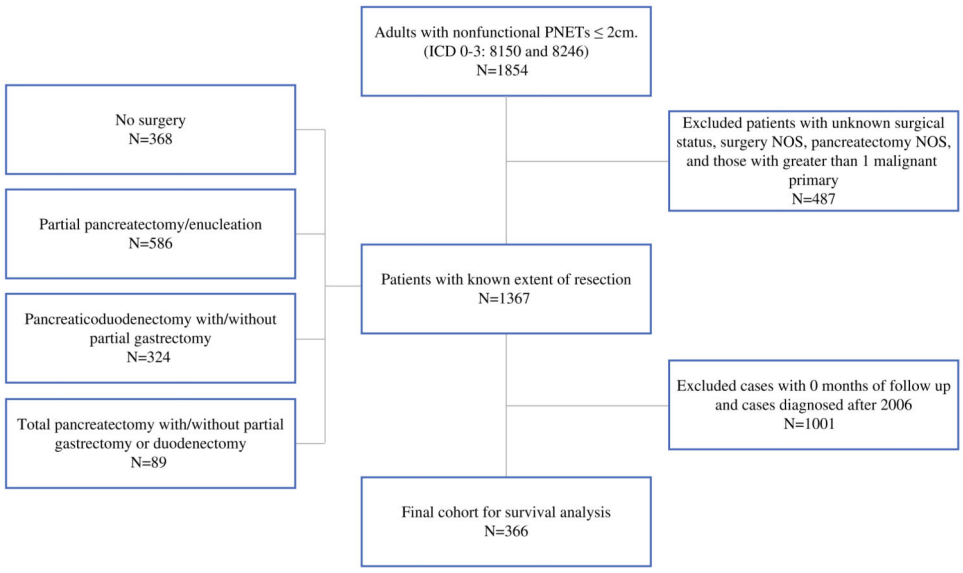

Fig. 1. Diagram of cohort inclusion and exclusion criteria for patients with nonfunctional PNETs ≤2 cm (NCDB 1998–2011)

NCDB= National Cancer Data Base, PNETs=pancreatic neuroendocrine tumors, ICD-0-3= International Classification of Diseases for Oncology, 3rd edition, NOS=not otherwise specified

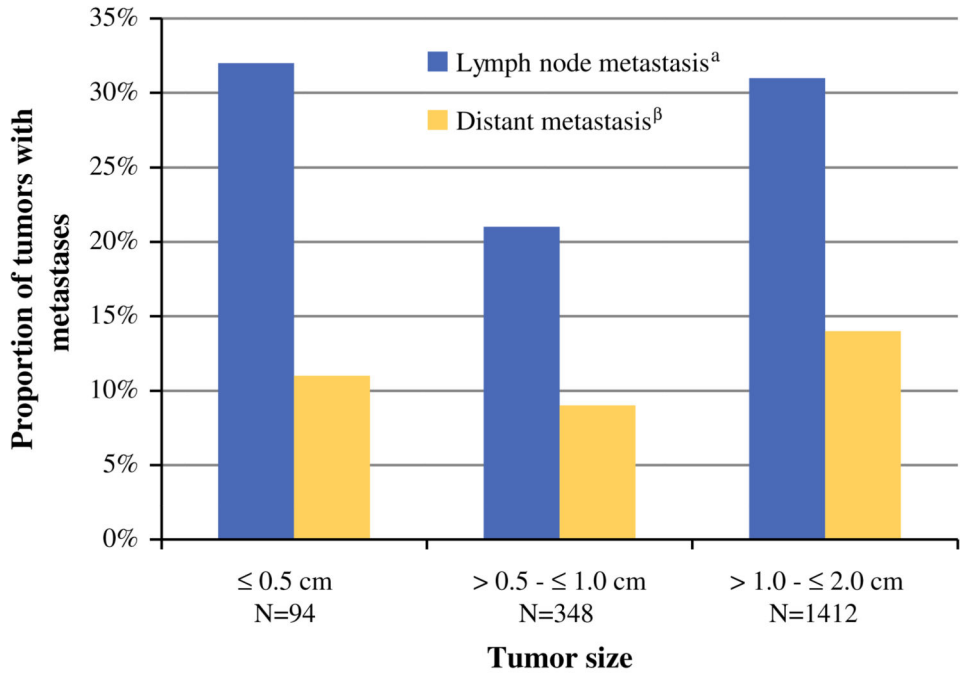

Fig. 2.

Rate of metastasis by tumor size for patients with PNETs ≤2 cm. [a]$p = 0.02$; variable has $n = 65$ missing. [β]$p = 0.02$; variable has $n = 813$ missing

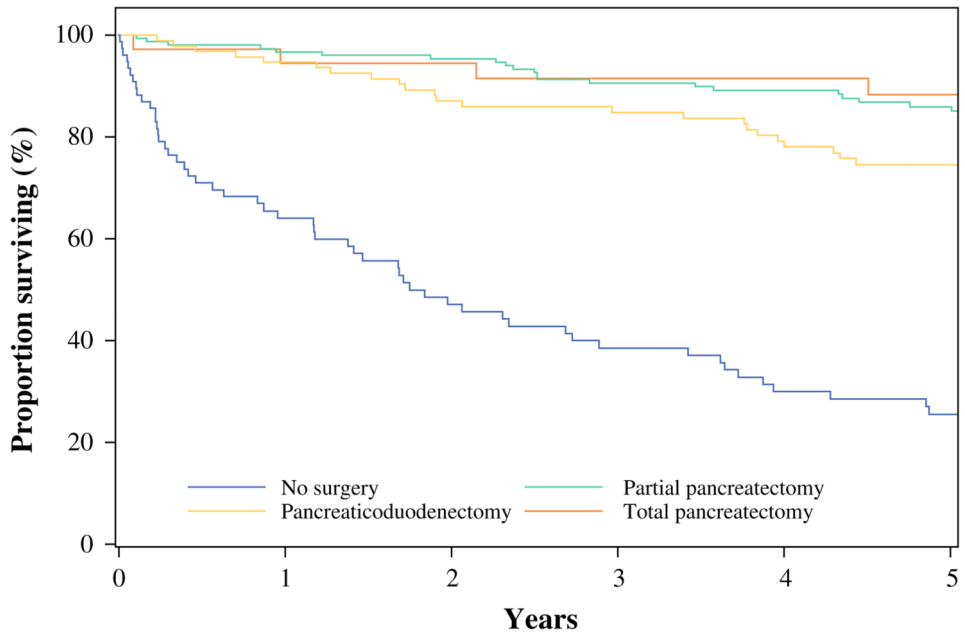

Fig. 3. OS by surgery type for patients with PNETs ≤ 2 cm

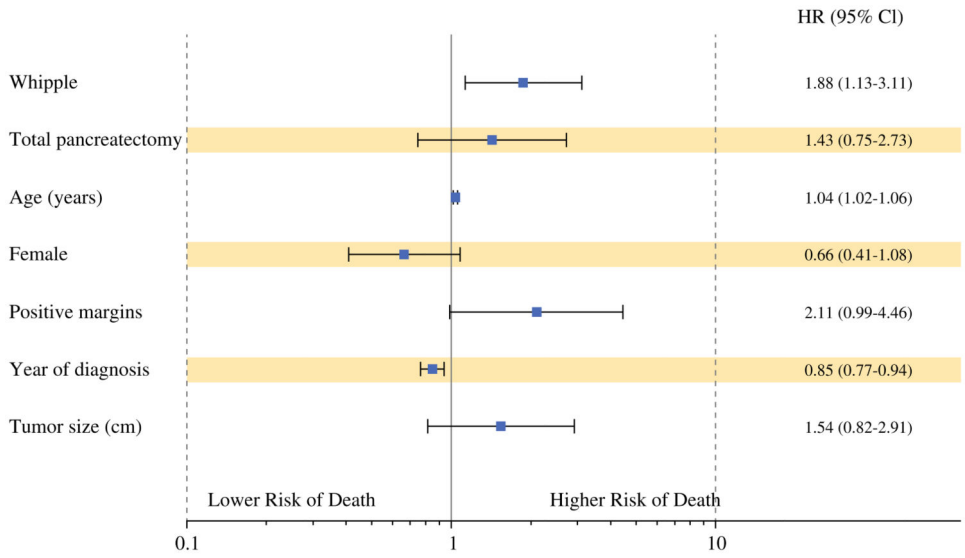

Fig. 4. Cox proportional hazard model of OS for patients undergoing treatment for PNETs ≤ 2 cm

Table 1

Baseline characteristics by surgery type for nonfunctional PNETs ≤2 cm

Characteristic	No surgery(*n* = 368)	Partial pancreatectomy(*n* = 586)	Pancreaticoduodenectomy(*n* = 324)	Total pancreatectomy(*n* = 89)	No surgery vs. any surgery *p* value	Between surgeries *p* value
Female gender (%)	55.7	55.3	56.5	55.1	0.99	0.94
Age at diagnosis (years)					<0.01	0.35
Median	63.0	57.0	56.0	56.0		
Q1, Q3	51.0, 73.5	47.0, 66.0	46.0, 64.0	46.0, 63.0		
Race (%)					0.92	0.22
White	85.3	86.7	83.3	87.5		
Black	14.4	12.5	16.7	12.5		
Other	0.3	0.7	0.0	0.0		
Charlson/Deyo score (%)					0.41	0.61
0	73.9	71.8	74.5	72.2		
1	18.9	22.1	19.9	25.3		
≥2	7.1	6.1	5.6	2.5		
Tumor size, cm					<0.01	<0.01
Median	1.6	1.5	1.5	1.5		
Q1, Q3	1.2, 2.0	1.0, 1.7	1.2, 1.9	1.1, 1.9		
Positive nodal status (%)	54.8	21.0	34.4	40.3	<0.01	<0.01
Distant metastases present (%)	42.1	2.0	1.6	1.1	<0.01	0.84
Grade (%)					<0.01	0.20
Well differentiated	52.0	86.5	85.3	85.5		
Moderately differentiated	15.7	10.6	7.8	8.1		
Poorly differentiated	29.9	1.8	5.2	4.8		
Undifferentiated	2.4	1.1	1.7	1.6		
Hospital type (%)					<0.01	0.91
Community cancer center	4.9	2.2	2.8	2.2		
Comprehensive cancer center	42.1	31.6	27.8	32.6		
Academic center	51.9	65.9	69.1	65.2		
Chemotherapy administered (%)	5.2	0.4	1.0	0.0	<0.01	0.37

Characteristic	No surgery(*n* = 368)	Partial pancreatectomy(*n* = 586)	Pancreaticoduodenectomy(*n* = 324)	Total pancreatectomy(*n* = 89)	No surgery vs. any surgery *p* value	Between surgeries *p* value
Radiotherapy administered (%)	3.3	1.7	2.2	3.4	0.16	0.58
Surgical margins positive (%)	–	9.0	4.1	3.5	–	0.01

Percentages do not include missing data. Missing data were <5 % except for the following variables: Charlson/Deyo score, 10 % missing; nodal status, 45 % missing; grade, 37 % missing; chemotherapy, 11 % missing; surgical margins, 29 % missing

PNET pancreatic neuroendocrine tumor