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Intratumoral Fibrosis and Tumor Growth Pattern as Prognostic Factors in Optimally Resected Pancreatic Neuroendocrine Neoplasms: An Analysis of 168 Cases

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Abstract

Objectives: Pancreatic neuroendocrine neoplasms (PanNENs) can recur after curative resection. We sought to establish the significance of tumor fibrosis and tumor growth pattern as predictors of recurrence free survival (RFS) and overall survival (OS).

Methods: A retrospective query of an institutional surgical database was performed from 2000–2018 to identify optimally resected PanNENs. All eligible slides were reviewed by an experienced gastrointestinal pathologist for established histopathologic prognostic factors as well as fibrosis and tumor growth pattern. We evaluated the effect of the interested variables through Cox proportional-hazards models.

Results: A hundred and sixty-eight cases were considered. The majority (90%) of patients had Grade 1 or 2 tumors, 46% showed significant fibrosis and 22% demonstrated an infiltrative growth pattern. Twenty-one percent of patients recurred. In multivariable analysis, lymphovascular invasion with a hazard ratio (HR) of 5.1 and infiltrative growth pattern (HR, 2.8) were significantly associated with increased risk of recurrence and increased risk of death (HR, 3.6 and 2.7 respectively). There was a significant decrease in RFS and OS for fibrosis and infiltrative growth pattern.

Conclusions: In optimally resected PanNENs, the presence of fibrosis and infiltrative growth pattern are significant risk factors for recurrence and/or decreased survival.

Keywords

neuroendocrine tumors; fibrosis; tumor growth pattern; recurrence

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Introduction

Neuroendocrine neoplasms (NENs) are rare malignancies that can arise in any tissue, but are most commonly found in the small bowel, pancreas, and lung.¹ Symptoms unfortunately can be absent for years and a good percentage of patients will present at an advanced stage and deemed incurable.² The delayed presentation of pancreatic NENs (PanNENs) presents a unique challenge for the treating oncologist. While metastatic patients can receive any of the FDA approved therapies, including everolimus,³ sunitinib,⁴ chemotherapy, or peptide receptor radionuclide therapy (PRRT),⁵ for resectable, early stage disease, the decision making process is more complicated. For example, for small PanNENs (less than 2 cm), surgery is not usually performed,⁶ but this concept is currently challenged^{7,8} by studies showing distinct high risk categories. For borderline resectable PanNENs, some but not all physicians choose neoadjuvant therapy,^{9,10} mirroring the treatment of pancreatic adenocarcinomas.

The majority of providers will not offer adjuvant treatment after what is deemed to be complete resection of a lesion, especially in patients who have undergone pancreaticoduodenectomy or total pancreatectomy. One of the reasons is that pancreatectomy is a specifically morbid and complex operation with post-operative complications ranging from 40-60%.¹¹ Unfortunately, close to 20% of patients¹² can recur even after extensive surgery; these are deemed incurable and will ultimately die of their disease. Given the gravity of pancreatic surgery and the implications of PanNEN recurrence, it is important to identify those high-risk individuals that would benefit from a neoadjuvant or adjuvant approach.

The most important prognostic indicator in PanNENs is the tumor classification (World Health Organization [WHO]), which incorporates the Ki-67 proliferative index, and categorizes these neoplasms into well-differentiated neuroendocrine tumors (NET), grades G1 to G3; and poorly differentiated neuroendocrine carcinomas (NEC)¹³; other established pathologic prognostic parameters are the tumor size and extrapancreatic extension (which are currently incorporated in staging) and lymphovascular invasion (LVI). Various groups have tried to attach prognostic significance to molecular alterations such as PTEN or PR expression¹⁴ or loss of heterozygosity for specific genes.¹⁵ In spite of these developments, the behavior of this group of tumors remains unpredictable. One potential way to improve our ability to identify at-risk individuals is to develop novel pathological markers. Previous reported studies have shown that NENs are associated with both regional and distant fibrosis^{16,17} which is attributed to the tumor microenvironment and secretion of specific hormones¹⁸ such as serotonin. Fibrosis is thought to play a significant, possibly protective role in the pancreatic adenocarcinoma counterpart¹⁹ but, despite some suggestive literature²⁰ its importance in resectable PanNENs has not been clarified. Additionally, the concept of tumor growth patterns has not been tested in NENs but has been shown to correlate with aggressiveness in multiple cancers including gastric,²¹ central nervous system,²² and sarcoma²³ and can influence recurrence and survival. Fibrosis and tumor growth patterns can be assessed from optimally sampled archival surgical pathology slides and thus lend themselves to retrospective evaluation. In this study, we sought to examine intratumoral

fibrosis and tumor growth patterns, as well as their association with recurrence and survival in PanNEN patients who were resected with a curative intent.

MATERIALS AND METHODS

Data Source

We performed a retrospective review of an institutional database of all adult patients who underwent a pancreatic resection with a curative intent for PanNENs at a single high-volume tertiary-care center from January 2000 to December 2018. Approval for the study was obtained from the Washington University Institutional Review Board. Information was retrospectively obtained from medical charts and no patients or family members were contacted. We retrieved all archival pathology slides from the original curative resections for review by an experienced gastrointestinal pathologist. We extracted the following variables from the patient's hospital chart: age at diagnosis, sex, race, body mass index (BMI), type of surgery, neoadjuvant treatment, recurrence status, and survival status. The tumor size, number of tumors, total number of lymph nodes examined, and total number of lymph nodes involved, were retrieved from the pathology reports. Only cases with unifocal tumors were considered in this cohort, since pathologic parameters could be variable in different tumors of the same patient.

Histologic Examination

All archival H&E stained slides as well as relevant immunohistochemical stains (neuroendocrine markers, Ki-67) were reviewed. The tumors were reclassified based on WHO 2017 grading scheme, based on morphology and Ki-67 proliferative index. All other established pathologic prognostic parameters were assessed, such as LVI, perineural invasion (PNI), and resection margin status. The Ki-67 index was estimated by manually counting 500–2000 cells on a print-out of the hotspot region using a color printer and calculating the percentage of Ki-67 stained cells compared to the total number of neoplastic cells. The morphology of the tumors was also reviewed to assess for the tumor growth pattern at the periphery. Most PanNENs lack a well-defined capsule. The tumors were classified as circumscribed, if there was an overall circumscription, but not necessarily encapsulation. Focal areas of tumor infiltration into the adjacent parenchyma, not exceeding 0.1 cm in depth, and not involving >10% of the circumference, were also considered as circumscribed. Infiltrative tumors on the other hand, showed multifocal irregular invasion into the pancreatic parenchyma or peripancreatic soft tissue, such that a delineation of the tumor area with adjacent normal was impossible in many areas along the periphery. For inclusion into this subtype, irregular invasion involving >0.1 cm in depth, and >10% of the circumference, were considered as criteria. Intratumoral fibrosis was assessed on H&E stained slides and was considered significant if fibrosis involved at least 10% of the entire tumor area. The cutoff was selected to ensure that fibrosis was not focal but significant and easily identifiable on visual examination. Dense hypocellular collagen bundles, imparting a pink appearance on H&E stain, was considered as mature fibrosis. Myxoid stroma, imparting a bluish-gray hue in the areas of fibrosis, associated with readily identifiable plump fibroblasts, when comprised at least 20% of the fibrosis, was considered a criterion for labeling the tumor to show immature fibrosis. The quantitative values assigned for the

assessment of tumor growth pattern and intratumoral fibrosis were arbitrary and incorporated the assessments of all available resection slides from each tumor. Eyeballing was used for these semi-quantitative estimations. To ensure reproducibility, a sample of the patients was independently assessed by a blinded second pathologist.

Statistical Analysis

The clinical characteristics were summarized using descriptive statistics. Recurrence-free survival (RFS) was defined as the time from the date of surgery to recurrence. Overall survival (OS) was defined as the time from the date of surgery to death from any cause. Alive patients were censored at the last follow-up. Kaplan-Meier (KM) curves for RFS and OS were generated to provide unadjusted survival estimates for the patients and across strata. Differences between strata were determined by log-rank tests. Cox proportional-hazards models were used to evaluate the relationship between the interested variables and both RFS and OS, respectively. The proportionality assumption was tested by adding a time-dependent covariate for each variable. The variables with $P < 0.20$ from univariate models were considered in the multivariable model. The final multivariable model was built using the backward stepwise selection approach to identify all significant risk factors. Factors significant at a 10% level were kept in the final model. The inapplicable or unknown values were excluded from both univariate and multivariable analysis. All statistical tests were two-sided using an $\alpha = 0.05$ level of significance. SAS Version 9.4 (Cary, NC) was used to perform all statistical analyses.

RESULTS

Patient Characteristics

A total of 168 patients had retrievable data (Table 1). Ninety-one 91 (54.2%) were male and 77 (45.8%) were female. Age range was 21–85 years with a median age of 59 years. Neoadjuvant treatment was given in 4 cases. The majority of patients were Caucasian (86.3%). The mean BMI was 29.7. Most patients underwent a pancreaticoduodenectomy or distal pancreatectomy (92% of aggregate cases). Tumor size ranged from 0.6 to 15.4 cm (median, 2.5 cm) and microscopically negative margins (R0 resection) were obtained in 89% of the cases; all other cases were R1 resections. A median of 14 lymph nodes (range, 0–47) were identified. LVI was identified in 41.7% cases, and PNI was identified in 34.5% cases. Reclassified according to the 2017 WHO scheme, 97.6% were well differentiated tumors (35.1% NET G1, 55.4% NET G2, and 7.1% NET G3), and only 2.4% cases were poorly differentiated carcinomas (NEC), all with large cell type histology. Seventy-eight tumors (46.5%) showed intratumoral fibrosis, of which 32% showed immature fibrosis. Growth pattern was described as infiltrative in 22.0% and circumscribed in 78.0% of the cases. Representative photomicrographs of tumors showing presence and absence of intratumoral fibrosis, as well as the tumor growth pattern, are shown in Figure 1. Median follow-up was 3.8 years to death or recurrence (range, 0.05–14.7). Thirty-six of 168 patients (21.4%) recurred and 29 (17.3%) expired. Interobserver agreement between pathology reviewers was high for both fibrosis (0.94 [95% confidence interval {CI}, 0.84–1.00]) and intratumoral growth assessment (0.85 [95% CI, 0.59–1.00]).

Analyses

In our cohort, patients with higher grade tumors had an increased chance of positive resection margins ($P = 0.04$), LVI ($P < 0.0001$), PNI ($P = 0.01$), infiltrative growth pattern ($P < 0.0001$), and lymph node involvement ($P = 0.0003$), but the tumor grade did not show any association with sex, size, race, age, BMI, or the type of surgery received. The presence of fibrosis had a positive association with LVI ($P < 0.0001$), PNI ($P = 0.0004$), with an increased Ki-67 value ($P = 0.02$), higher WHO grade (NET G3 and NEC; $P = 0.04$), as well as with the number of positive lymph nodes in the resection specimen ($P < 0.0001$). Fibrosis was also strongly associated with an infiltrative growth pattern ($P < 0.0001$) as well as the type of surgery received (tumors excised by Whipple procedure had significantly more fibrosis than those which were removed by distal pancreatectomy and others with $P = 0.02$; likely implying that tumors located in the head of the pancreas show more fibrosis than those of the body and tail). Intratumoral fibrosis did not show any correlation with age at diagnosis, sex, race, BMI, tumor size, or status of resection margins. It also did not show a correlation with neoadjuvant therapy received. Infiltrative growth pattern was associated with LVI, increased Ki-67, PNI, lymph node involvement, and higher WHO grade (all with $P < 0.0001$), but the growth pattern did not show any association with age at diagnosis, race, sex, BMI, tumor size, resection margin status, status of neoadjuvant therapy, or the type of surgery received.

Figure 2 shows K-M plots for RFS and OS by the tumor growth pattern. Figure 3 shows K-M plots for RFS by the status of fibrosis. The survival analysis through Cox proportional-hazards models are shown in Table 2. The Ki-67 index, WHO grade, LVI, PNI, and the tumor growth pattern were significant predictors of both OS and RFS in univariate analysis. In addition, while status of fibrosis and lymph node involvement were also significant predictors of RFS ($P = 0.0031$ and 0.03), status of fibrosis did not reach statistical significance in OS ($P = 0.18$). On multivariable analysis, LVI and an infiltrative growth pattern were independent predictors of both tumor recurrence and death. In addition, in our cohort, the Ki-67 index was a significant predictor of RFS, and age at diagnosis was a significant predictor of OS. We also ran separate analyses excluding high grade patients, as well as patients with LVI and neoadjuvant treatment. The results remained unchanged except that tumor growth pattern did not reach statistical significance for OS.

DISCUSSION

Despite recent advances, PanNENs remain notoriously difficult to treat. In early stages, major surgery can significantly prolong survival, but metastatic patients have a dismal prognosis¹ with a median OS of only 2 years. Unfortunately, even extensive resections cannot guarantee a cure^{8,12} and can be associated with significant morbidity.¹¹ The current guidelines do not routinely advocate for adjuvant treatment of optimally resected PanNENs. In our cohort of localized cases, the overwhelming majority of the patients had R0 resections and G1/G2 disease; despite that, about 20% recurred, consistent with previously published data and 80% of the patients with recurrence have expired. It is thus imperative to identify the patients who are at highest risk for recurrence and could benefit from different surveillance or treatment strategies.

The literature has pointed to a variety of prognostic factors in NEN patients of all stages; these include age, performance status, grade and metastases.^{13,24,25} Our analysis has focused on a generally considered ideal population- mainly low to intermediate PanNEN patients resected in a major academic institution- and has identified a high Ki-67, presence of LVI and PNI, infiltrative growth pattern, and fibrosis as significant risk factors associated with disease recurrence and/or death. A higher Ki-67 (>5%)¹² and positive margins, as well as T and N status²⁶⁻²⁹ and PNI³⁰ have been associated with recurrence before in optimally resected PanNEN patients, but we were able to show that LVI is also a significant prognostic factor (especially in cases where there is no LN sampling). Moreover, in our optimally resected population, grading did not retain its significance in multivariable analysis. Grading is a well-established prognostic factor for NEN, but retrospective data² show a remarkable survival advantage in localized tumors regardless of grade. Therefore, we feel it plays a much more prominent role upon established metastasis and its effect is diluted in optimally cytoreduced cases.

On the other hand, the importance of mature and immature fibrosis in pathology specimens is relatively newer knowledge in PanNENs. Fibrosis in pancreatic adenocarcinomas has been associated with chemoresistance and poor prognosis in preclinical models^{31,32} and pancreatic stromal targeting^{33,34} has been attempted in some clinical trials to increase chemosensitivity. Nodular fibrosis was described as one of the adverse prognostic factor in a retrospective series²⁰ but this study did not differentiate between mature and immature variants, included metastatic and nonmetastatic PanNENs and stratified tumors according to WHO 2004 criteria. Tumor infiltrating growth patterns have also been associated with cancer virulence in a variety of tumors^{21-23,35} but have similarly never been described in the PanNEN literature. One thought is that that an infiltrative pattern is indicative of a rapidly growing, less organized tumor and thus is associated with worse outcomes. In our analyses the presence of an infiltrative pattern was significantly associated with LVI, PNI, lymph node involvement, and Ki-67, consistent with a more aggressive tumor spread pattern, and the majority of patients who recurred had fatal outcomes. The assessment of intratumoral fibrosis as well as tumor growth pattern was based on a semi-quantitative method and involved eyeball estimation of routine H&E slides. This makes an easy implementation of these novel pathologic prognostic factors in routine clinical cases.

The implications of these findings are readily apparent and raise the question of adjuvant treatment in high risk disease, an approach used in a variety of cancers, including colon³⁶, pancreatic adenocarcinoma³⁷ or even resected high grade NENs.³⁸ Most low grade PanNEN patients are observed after curative resection with suggested reimaging within 1 year as recommended by National Comprehensive Cancer Network (NCCN) guidelines.³⁸ Our results suggest that the subgroup of patients whose tumors exhibit fibrosis, LVI and infiltrative growth are at higher risk of recurrence and would ideally benefit from a more aggressive imaging or possibly adjuvant treatment, in order to prevent recurrences or treat them at an early stage.

Our analysis has quite a few limitations. It is a retrospective nonrandomized study of medically fit patients who underwent surgery in a tertiary center; this introduces a good amount of bias. Our cohort included some high-grade patients who were included in the

analysis; grade did not hold up as a significant factor in the OS multivariable model for those optimally resected patients. Estimation of fibrosis and tumor growth pattern was purposefully simple and subjective, as we tried to incorporate an easy test into the management of these complicated tumors. We were unable to collect genomic data or information on subsequent therapies for recurrent cases. Moreover, for some of the patients treated in the prior years, there was limited or no option for detailed somatostatin receptor imaging with a Ga-Dotatate positron emission tomography/computed tomography scan, a modality that is quite efficient at pinpointing distant metastases and classifying more patients as unresectable due to distant disease. While we were able to demonstrate the significance of both fibrosis and tumor growth pattern for RFS, only growth pattern held up in the OS multivariable analysis. This could be explained by the limited number of cases, the limited follow-up interval, or the variation in palliative treatments for these metastatic patients. However, we believe that on top of well described parameters such as stage, differentiation and proliferation markers, tumor fibrosis and infiltrative growth pattern should be recorded in curatively resected PanNENs in order to identify the subset of patients who might need close follow-up and possibly adjuvant treatment. The latter should ideally be explored in a prospective randomized study. Our data for now is hypothesis-generating and could be used to examine the importance of tumor microenvironment on the virulence of PanNENs, as well as help stratify curatively resected patients in various risk categories.

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FIGURE 1.

Representative photomicrographs demonstrating intratumoral fibrosis and tumor growth pattern. A: Tumor with no fibrosis (top left), and a circumscribed growth pattern (interface with normal pancreatic stroma, bottom right); B: Tumor with infiltrative growth pattern and mature stromal fibrosis; C: immature fibrosis with stromal mucinosis; D: mature fibrosis with collagenous stroma within the tumor, and a circumscribed interface with pancreatic parenchyma

FIGURE 2.
Tumor growth pattern and survival (left: RFS; right: OS)

FIGURE 3.
Fibrosis with RFS (left: fibrosis vs. no fibrosis; right: immature fibrosis, vs. mature fibrosis, vs. no fibrosis)

TABLE 1.**Patient Characteristics**

Demographic and Clinicopathologic Parameter	No. Patients (%)
Sex	
Male	91 (54.2)
Female	77 (45.8)
Race	
White	145 (86.3)
African American	20 (11.9)
Asian	2 (1.2)
Other	1 (0.6)
Surgery type	
Whipple	69 (41.1)
Distal	86 (51.2)
Central	6 (3.6)
Local Enucleation	3 (1.8)
Local Excision	3 (1.8)
Total Pancreatectomy	1 (0.6)
Neoadjuvant treatment	
No	164 (97.6)
Yes	4 (2.4)
WHO 2017 grade	
NET G1	59 (35.1)
NET G2	93 (55.4)
NET G3	12 (7.1)
PD NEC	4 (2.4)
Margins	
Positive	19 (11.3)
Negative	149 (88.7)
LVI	
No	98 (58.3)
Yes	70 (41.7)
PNI	
No	110 (65.5)
Yes	58 (34.5)
Fibrosis	
No fibrosis	90 (53.6)
Mature fibrosis	53 (31.6)
Immature fibrosis	25 (14.9)
Growth pattern	
Circumscribed	131 (78.0)
Infiltrative	37 (22.0)

TABLE 2.
Univariate and Multivariable Analysis for Recurrence Free Survival (RFS) and Overall Survival (OS)

Parameter	RFS			OS		
	Univariate HR (95% CI)	P	Multivariable HR (95% CI)	Univariate HR (95% CI)	P	Multivariable HR (95% CI)
Age at diagnosis	0.990 (0.968–1.013)	0.3978		1.022 (0.993–1.052)	0.1461	1.035 (1.002–1.070)
Ki-67 index	1.045 (1.029–1.062)	<0.0001	1.024 (1.005–1.043)	1.039 (1.016–1.062)	0.0007	
Male vs Female	1.479 (0.749–2.921)	0.2598		1.017 (0.480–2.155)	0.9651	
NET G1 vs NET G3/NEC	0.023 (0.005–0.106)	<0.0001		0.085 (0.025–0.288)	<0.0001	
NET G2 vs NET G3/NEC	0.157 (0.073–0.338)	<0.0001		0.168 (0.070–0.402)	<0.0001	
LVI, yes/no	10.733 (4.169–27.630)	<0.0001	5.133 (1.607–16.394)	5.215 (1.980–13.736)	0.0008	3.592 (1.198–10.768)
PNL, yes/no	3.903 (1.947–7.825)	0.0001		2.518 (1.176–5.393)	0.0175	
Tumor growth pattern, infiltrative vs circumscribed	7.304 (3.727–14.313)	<0.0001	2.814 (1.211–6.538)	4.372 (2.038–9.375)	0.0002	2.720 (1.150–6.433)
Intratumoral fibrosis, yes/no	2.924 (1.438–5.947)	0.0031		1.709 (0.783–3.731)	0.1787	
Whipple vs non-Whipple				1.397 (0.661–2.953)	0.3807	
Tumor size	1.050 (0.956–1.154)	0.3701		0.964 (0.830–1.118)	0.6247	