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ORIGINAL ARTICLE – PANCREATIC TUMORS

Malignant Solid Pseudopapillary Neoplasm of the Pancreas: An Orthogonal Analysis

Andrew M. Fleming, MD[1,2], Leah E. Hendrick, MD, MS[1], Danny Yakoub, MD, PhD[3], Hafeez Abdelhafeez, MD[1,2], Jeremiah L. Deneve, DO[4], Max R. Langham Jr., MD[1,2], Evan S. Glazer, MD, PhD[1], Andrew M. Davidoff, MD[1,2], Nipun B. Merchant, MD[5], Paxton V. Dickson, MD[1], and Andrew J. Murphy, MD[1,2]

[1]Department of Surgery, The University of Tennessee Health Science Center, Memphis, TN; [2]Department of Surgery, St. Jude Children's Research Hospital, Memphis, TN; [3]Department of Surgery, Augusta University Medical Center, Augusta, GA; [4]Department of Surgery, University of North Carolina, Chapel Hill, NC; [5]Department of Surgery, University of Miami Health System, Miami, FL

ABSTRACT

Background. Pancreatic solid pseudopapillary neoplasms (SPN) are generally indolent; however, some patients present with "malignant" SPN. An orthogonal analysis of multiple datasets was performed to investigate the utility of complete surgical resection (CSR) for malignant SPN.

Methods. A systematic review was performed for cases of malignant SPN, defined as T4, N1, and/or M1. Malignant SPN was analyzed within the National Cancer Database (NCDB) and compared with T1-3N0M0 SPN. Predictors of malignant SPN were assessed, and treatments were analyzed by using survival analysis.

Results. The systematic review yielded 164 cases of malignant SPN. Of 31 children, only one died due to malignant SPN. Among adults, CSR was associated with improved disease-specific survival (DSS) ($P = 0.0002$). Chemotherapy did not improve malignant SPN DSS, whether resected ($P = 0.8485$) or not ($P = 0.2219$). Of 692 adults with SPN within the NCDB, 93 (13.4%) had malignant SPN. Pancreatic head location (odds ratio [OR] 2.174; 95% confidence interval [CI] 1.136–4.166; $P = 0.0186$) and tumor size (OR 1.154; 95% CI 1.079–1.235; $P < 0.0001$) associated with the malignant phenotype. Malignant SPN predicted decreased overall survival (OS) compared with T1-3N0M0 disease ($P < 0.0001$). Resected malignant SPN demonstrated improved OS ($P < 0.0001$), including resected stage IV malignant SPN ($P = 0.0003$). Chemotherapy did not improve OS for malignant SPN, whether resected ($P = 0.8633$) or not ($P = 0.5734$). Within a multivariable model, resection was associated with decreased hazard of death (hazard ratio 0.090; 95% CI 0.030–0.261; $P < 0.0001$).

Conclusions. Approximately 13% of patients with SPN present with a malignant phenotype. Pediatric cases may be less aggressive. Resection may improve survival for malignant SPN, which does not appear chemosensitive.

Paxton V. Dickson and Andrew J. Murphy have contributed equally to this work and are co-senior authors.

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A. M. Fleming, MD
e-mail: aflemin8@uthsc.edu

Solid pseudopapillary neoplasm of the pancreas (SPN) comprises less than 2% of all pancreatic tumors.[1] SPN demonstrates a tenfold higher incidence in females and represents the most common pancreatic tumor in childhood.[2–4] First reported in 1959, SPN was designated a low-grade pancreatic malignancy by the World Health Organization in 1996.[5,6] SPN is associated with a favorable prognosis, and organ-preserving surgical resection can provide excellent recurrence-free survival.[1,7]

Some SPN demonstrate a more aggressive phenotype with extra-pancreatic extension, invasion of adjacent organs, vascular encasement, lymph node metastases, distant metastatic disease, disease relapse, and/or disease-specific mortality.[8–10] These cases are sometimes referred to as "malignant" SPN. Predictors of the malignant SPN phenotype, and its impact on disease-specific survival (DSS) are not well-defined.[8,11–13] Some data have suggested that malignant SPN in children follows a fairly indolent course, even with distant metastatic disease.[3,4,8] No consensus guidelines regarding the treatment of malignant SPN currently exist. Data supporting complete surgical resection (CSR) of metastatic disease and the utility of adjuvant therapies in patients with distant metastases remain anecdotal.[14,15] In these contexts, an orthogonal approach to data analysis can incorporate multiple comparative analyses of independent data sources to add validity to the results of each individual analysis.[16,17] This methodology increases the reliability of the results of each analysis and is seen as a means of "cross checking" the results of one analysis against another independent analysis within the same scientific experiment.[16,17]

The current study comprises an orthogonal analysis of multiple datasets to further characterize the natural history and optimal treatment of malignant SPN.[16] The first goal of this study was to perform a systematic review and pooled data analysis of all reported cases of malignant SPN in children and adults. These data were used to compare the disease-specific survival (DSS) of pediatric and adult patients and to assess the impact of CSR on disease-specific survival (DSS) for patients with malignant SPN. The second goal of this study was to identify cases of malignant SPN among all cases of SPN within the National Cancer Database (NCDB). These data were used to identify predictors of the malignant SPN phenotype and further validate the utility of surgical resection in the setting of metastatic disease. The third goal was to use each dataset to evaluate the utility of adjuvant treatments for malignant SPN, including the use of systemic chemotherapy and non-surgical liver-directed therapies for unresected liver metastases.

METHODS

Institutional Review Board Approval and Prospective Registration

The University of Tennessee Health Science Center Institutional Review Board (IRB) determined this study to be Not Human Subjects Research (NHSR) status (IRB number: 22-08891-NHSR). This study was prospectively registered through the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42022349312).

Systematic Review of Reported Malignant SPN Cases—Eligibility Criteria

Reported cases were defined as having "malignant SPN" if they had T4 tumors according to the American Joint Committee on Cancer (AJCC) 8th edition staging system, AND/OR if they had lymph node metastases (N1), AND/OR if they had distant metastatic disease (M1). Unresected cases reported in the literature determined to be T4 were clinically staged or noted to be T4 based on the intraoperative findings. Resected tumors were pathologically staged. All cases meeting these staging criteria were included for analysis. Cases were excluded from pooled analysis if the patients had T1-3N0M0 disease (not the malignant SPN phenotype), if there were no treatment data (manuscripts purely focused on histopathology), or if relevant patient data were not available in the English language.

Systematic Review of Reported Malignant SPN Cases—Information Sources

PubMed, MEDLINE, EMBASE, the Cochrane database, and SCOPUS were systematically reviewed for all reported cases of malignant SPN. The international prospective register of systematic reviews (PROSPERO) was analyzed for reviews of similar scope. All publication dates from 1959 onward were included in the search, with the final query performed on July 22, 2022.

Systematic Review of Reported Malignant SPN Cases—Search Strategy

The text words "solid pseudopapillary neoplasm," "solid pseudopapillary tumor," and "pancreas," and the medical subjects headings (MeSH) terms "Pancreas" and "Neoplasm" were used alone and in combination with the text "Metastatic Disease," "Metastasis," and the MeSH term "Metastasis" using the Boolean logic term "OR." The search was augmented by using the Boolean logic term "AND" to add the terms text words "Metastasis," "Liver Metastasis," "Lymph Node Metastasis," and "Distant Metastasis." The "case reports" and "review" filter options were toggled to refine the search further. A thorough review of all citations and abstracts identified was performed, and the search was expanded via the "related articles" function. The bibliographies of all retrieved papers were screened for additional eligible literature. The prospectively registered search strategy document can be found on PROSPERO for a complete list of search terms used in this analysis (https://www.crd.york.ac.uk/PROSPEROFILES/349312_STRATEGY_20220726.pdf).

Systematic Review of Reported Malignant SPN Cases—Selection Process

Selected studies underwent detailed review to determine if they met inclusion criteria. The predetermined protocol for disagreements regarding inclusion of a study consisted of resolution by consensus or by the decision of a third reviewer.

Systematic Review of Reported Malignant SPN Cases—Data Collection Process

After the selection process, data were abstracted regarding the primary data items of interest in each of the included studies (achievement of CSR, DSS in months). Study characteristics were abstracted into the standardized data collection spreadsheet (first author, year of publication, location of study institution, journal of publication). Important patient, tumor, and treatment data also were abstracted, including patient age, patient biological sex, presence of locally invasive disease, presence of nodal metastases, presence of distant metastatic disease, timing of metastatic disease, location of metastatic disease, receipt of systemic therapy, and receipt of nonsurgical liver-directed therapy.

Systematic Review of Reported Malignant SPN Cases of Data Items

Reported cases were defined as having "malignant SPN" if they had T4 tumors according to the American Joint Committee on Cancer (AJCC) 8th edition staging system (invading adjacent celiac axis or superior mesenteric artery), AND/OR demonstrated invasion of adjacent organs (stomach, duodenum, colon, porta hepatis), AND/OR had nodal metastases (N1), AND/OR if they had distant metastatic disease (M1). CSR designation was applied to a reported case of malignant SPN when the included operative description recorded resection of all reported disease for that patient. Patients who underwent resection of their primary tumors, but not metastatic disease, were not denoted "CSR." Patients were denoted "pediatric patient" status if under the age of 18 years.

Primary data items of interest included the following:

- Complete surgical resection (CSR)
- Disease-specific survival in months

Secondary data items of interest included the following:

- Patient data
    - Patient age
    - Patient biological sex
- Disease data
    - Presence of extra-pancreatic tumor extension into adjacent vascular structures and/or adjacent organs (T4 disease)
    - Presence of lymph node metastases (N1 disease)
    - Presence of distant metastatic disease (M1 disease)
    - Synchronous vs. metachronous metastatic disease
    - Location of metastatic disease (liver, peritoneum, lung, other)
- Treatment data
    - Extent of pancreatectomy (local excision/enucleation, distal pancreatectomy, pancreatoduodenectomy, total pancreatectomy, multivisceral resection)
    - Extent of hepatectomy (nonanatomic wedge resection, segmentectomy, sectionectomy, hemihepatectomy, trisectionectomy, total hepatectomy with transplantation), if applicable
    - Receipt of systemic chemotherapy
    - Receipt of nonsurgical liver-directed therapy (transcatheter arterial chemoembolization, bland transarterial embolization, radiofrequency ablation, hepatic artery infusion)

Systematic Review of Reported Malignant SPN Cases—Study Risk of Bias Assessment

This analysis intrinsically contained a high risk of both selection and reporting bias given the nonstandardized nature of case reports and case series. The Joanna Briggs Institute critical appraisal checklist for case reports was used as a reference to assess the quality of included cases.[18]

National Cancer Database—Data Source and Patient Selection

The NCDB is estimated to include most cancer cases in the United States and functions as a joint endeavor of the American College of Surgeons Commission on Cancer and the American Cancer Society. Cases within the NCDB are classified using the International Classification of Disease for Oncology (ICD-O-3) histology codes. Cases were included for analysis from the 2004-2017 Pancreas dataset if they had ICD-O-3 codes corresponding to "Solid Pseudopapillary Neoplasm of the Pancreas" (ICD-O-3 8452). Patients with all other histology codes were excluded from this analysis, as were patients with incomplete staging data. Cases of SPN in the NCDB were defined as having "malignant SPN" if they had T4 tumors, OR if they had lymph node metastases (N1), OR if they had distant metastatic disease (M1).

Statistical Analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and GraphPad Prism Version 9.4.0 (GraphPad Software, LLC., San Diego, CA). Data from the systematic review were analyzed independently from those abstracted from the NCDB. Patient characteristics, tumor characteristics, treatment data, and outcomes data were tabulated with descriptive statistics. Data from the systematic review were analyzed as disease-specific survival (DSS), while data from the NCDB were analyzed as overall survival (OS), as data regarding disease relapse and cause of death are not provided within the NCDB. Variables associated with increased hazard of death were analyzed with univariable and multivariable Cox proportional hazards models. Patients with data missing for variables incorporated in the multivariable model were excluded from multivariable analysis. Survival curves were generated by using the Kaplan-Meier method, stratified by relevant variables, and compared by using log-rank tests. The incidence of malignant SPN was analyzed over time in both datasets by using one-way ANOVA with testing for linear trend. All hypothesis testing was two-sided. P values < 0.05 were considered statistically significant for all analyses.

RESULTS

Systematic Review of Reported Cases of Malignant SPN—Study Selection

Complete details regarding the results of the study selection process are depicted in Fig. 1A. A total of 665 records were initially identified in our systematic review. Of these, 428 were found to be off-topic or duplicate publications. A total of 237 studies were reviewed in more detail. Of these, 97 studies were excluded as they did not meet criteria for malignant SPN status, whereas 46 did not have patient data available in the English language. All 94 reports sought for retrieval were successfully retrieved via institutional access or institutional interlibrary loan and document delivery systems. Ninety-four publications were included for analysis, comprising 164 total cases of malignant SPN.[1,9,10,19–109] Details regarding all included studies can be found in Supplemental Table S1.

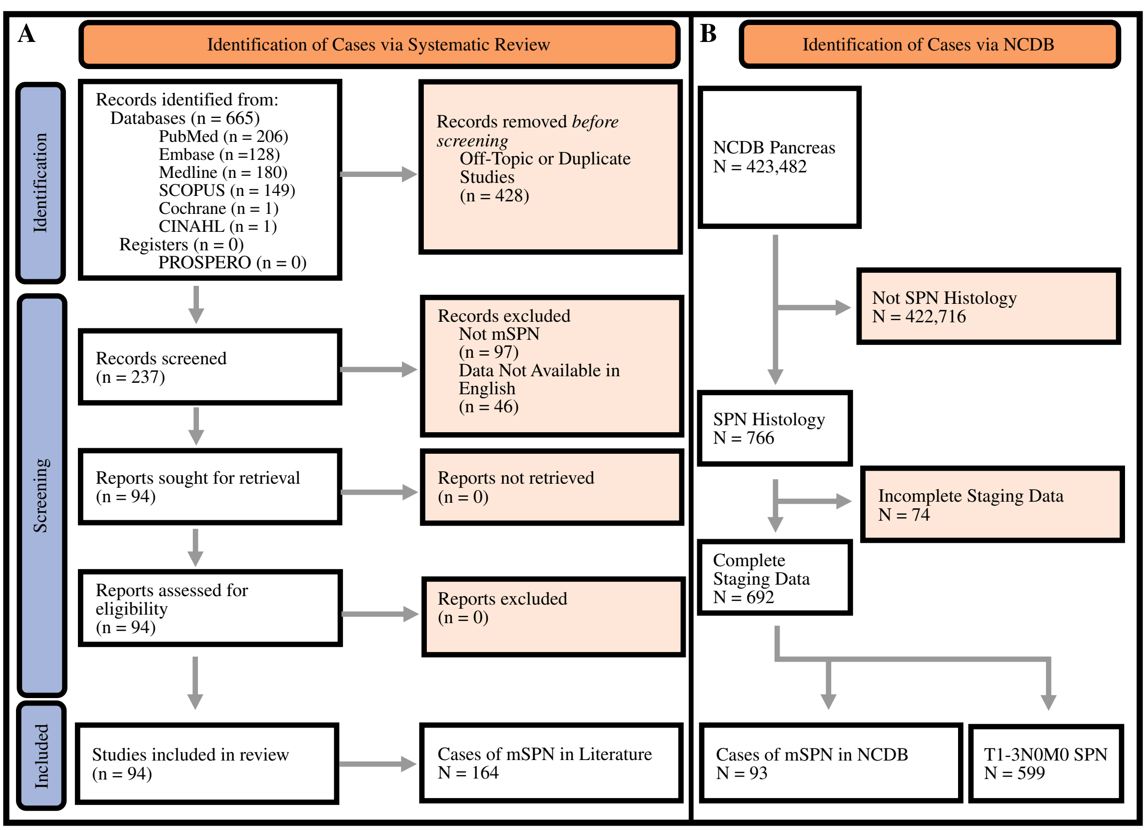

FIG. 1 Case selection flow diagram from **A** the systematic review of reported cases and **B** the National Cancer Database. Adapted from Page et al.[120] mSPN malignant SPN

Systematic Review of Reported Malignant SPN Cases—Patient Characteristics, Tumor Characteristics, and Treatment Data

A total of 164 reported cases of malignant SPN from Austria, Canada, China, Croatia, France, Germany, Hong Kong, India, Italy, Japan, Korea, Pakistan, Poland, Portugal, Puerto Rico, Singapore, South Africa, Spain, Sri Lanka, Switzerland, Turkey, the United Kingdom, and the United States of America were included for analysis (Table 1). Patients with malignant SPN were a median age of 39.0 years (interquartile range [IQR] 20.0–50.0), with 31 patients younger than age 18 years captured in the review. There were 142 female patients with malignant SPN (86.6%). Sixty-eight patients had locally invasive disease, consisting of T4 tumors with invasion into adjacent vascular structures or organs (41.5%), and 144 patients had metastatic disease (87.8%). Of these 144 patients, 79 had metastases at diagnosis (56.9%), whereas 62 were noted to have metastases at time of disease relapse (43.1%). The most common sites of metastases were the liver (n = 123), peritoneum (n = 34), and lymph nodes (n = 19). CSR was reported in 92 patients (56.1%). Thirty-one patients received systemic therapies (18.9%), and 37 patients underwent nonsurgical liver directed therapies (22.6%). A detailed treatment analysis flow diagram can be found in Supplemental Fig. S1. Reported cases of malignant SPN in the surgical literature were not found to be significantly increasing over time within the publication period of 1980–2022 (P = 0.4158).

Systematic Review of Reported Malignant SPN Cases—Disease-Specific Survival Analysis

One-year, 5-year, and 10-year DSS for the entire cohort were 94.3% (95% CI 88.9–97.1%), 81.2% (95% CI 71.9–87.7%), and 71.0% (95% CI 57.5–80.9%), respectively (Fig. 2A). Adult patients had a significantly decreased 10-year DSS of 62.6% (95% CI 44.8–76.1%) compared with children, who had a 96.4% (95% CI 77.2–99.5%) 10-year DSS (log-rank P = 0.0248) (Fig. 2B). One pediatric death attributable to malignant SPN was captured within the current study's systematic review.[44] Among 99 adult patients with malignant SPN and complete survival data, CSR was associated with a significant improvement in DSS (log-rank P = 0.0002; Fig. 2D). Receipt of systemic therapy was not associated with improved DSS for adults who underwent incomplete resection (log-rank P = 0.2219; Fig. 2E) or CSR (log-rank P = 0.8485; Fig. 2E). Subgroup analysis of adult patients with unresected liver metastases revealed that nonsurgical liver-directed therapies were not associated with a

TABLE 1 Patient characteristics, disease characteristics, and details of treatment for 164 reported cases of malignant solid pseudopapillary neoplasm of the pancreas (malignant SPN)

Variable	Reported malignant SPN cases (n = 164)
Patient age in diagnosis in years, median [IQR]	39.0 [20.0–50.0]
Pediatric patient status,* n (%)	
Age ≥18	116 (72.0%)
Age <18	31 (17.4%)
Unknown	17 (10.6%)
Biological sex, n (%)	
Female	142 (86.6%)
Male	13 (7.9%)
Unknown	9 (5.5%)
Locally invasive disease, n (%)	68 (41.5%)
Metastatic disease, n (%)	144 (87.8%)
Synchronous metastases, n (% of metastatic disease)	82 (56.9%)
Metachronous metastases, n (% of metastatic disease)	62 (43.1%)
Time to metachronous metastases in months, median [IQR]	48.0 [24.0–87.0]
Liver metastases, n (%)	123 (75.0%)
Lymph node metastases, n (%)	19 (11.6%)
Peritoneal metastases, n (%)	34 (20.7%)
Complete surgical resection achieved, n (%)	92 (56.1%)
Systemic therapy, n (%)	31 (18.9%)
Nonsurgical liver directed therapy, n (%)	37 (22.6%)

*Pediatric patient status was denoted when the patient's age was <18 years; n number; *IQR* interquartile range

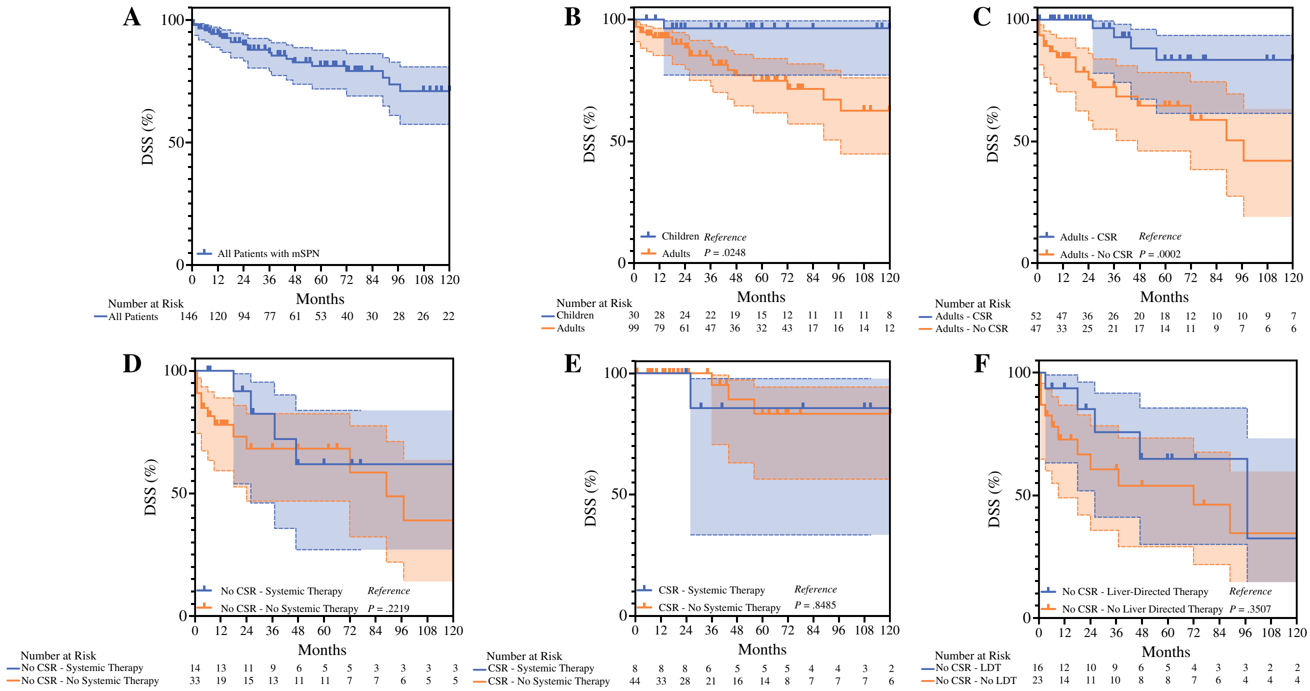

FIG. 2 Disease-specific survival of **A** all patients in the cohort stratified by **B** pediatric patient status. DSS of adult patients stratified by **C** receipt of complete surgical resection, **D** receipt of systemic therapy in the absence of complete surgical resection, **E** receipt of systemic therapy after complete surgical resection, and **F** receipt of non-surgical liver-directed therapies in the setting of unresected liver metastases. *mSPN* malignant SPN

significant difference in DSS (log-rank $P = 0.3507$; Fig. 2F). The impact of CSR, systemic therapies, and liver-directed therapies were not evaluated for pediatric patients given the low event rate of patient mortality.

National Cancer Database—Patient Characteristics, Tumor Characteristics, and Treatment Data

Complete details regarding the results of the NCDB case selection process are depicted in Fig. 1B. Among 692 cases of SPN included from the NCDB for analysis, 93 patients had a malignant phenotype, consisting of T4 disease, N1 disease, and/or M1 disease (13.4%; Table 2). All other patients (599/692) had T1-3N0M0 disease and were determined to not possess the malignant SPN phenotype. Patients with malignant SPN were older (44 vs. 35 years, $P < 0.0001$) and more often male (28.0% vs. 13.0%, $P = 0.0005$). Fewer patients with malignant SPN had private insurance (49.5% vs. 62.6%, $P = 0.0028$). Patients with malignant SPN had a larger median tumor size (8.0 cm vs. 4.5 cm, $P < 0.0001$), less often presented with tumors in the body or tail of the pancreas (37.6% vs. 58.9%, $P < 0.0001$), and less often underwent distal pancreatectomy for their primary tumors (22.6% vs. 50.6%, $P < 0.0001$). Among resected patients, those with malignant SPN had more lymph nodes examined (11.0 vs. 8.0, $P = 0.0028$) and more often received systemic chemotherapy (29.0% vs. 3.0%, $P < 0.0001$). Postoperative length of stay was longer in the malignant SPN group (7.0 vs. 6.0 days, $P = 0.0340$). Within a multiple logistic regression model accounting for age, sex, insurance status, tumor location, and tumor size, only tumor location in the pancreatic head (odds ratio (OR) 2.174; 95% CI 1.136-4.166, $P = 0.0186$) and increasing tumor size (OR 1.154 per cm; 95% CI 1.079-1.235; $P < 0.0001$) were significantly associated with increased risk of a malignant phenotype for patients with SPN (Table 3). A complete treatment analysis flow diagram for the OS analyses of the NCDB cohort can be found in Supplemental Fig. S2. Test for linear trend revealed that the incidence of the malignant SPN phenotype was found to be significantly increasing over time within the NCDB ($P = 0.0027$).

National Cancer Database—Overall Survival Analysis

One-year, 5-year, and 10-year OS for the entire cohort were 96.4% (95% CI 94.5–97.7%), 91.4% (95% CI 88.3–93.8%), and 85.5% (95% CI 80.7–89.2%; Fig. 3A). Patients with malignant SPN had significantly decreased OS compared with patients with T1-3N0M0 disease (log-rank $P < 0.0001$; Fig. 3B). One-year, 5-year, and 10-year OS for patients with malignant SPN versus T1-3N0M0 disease were 77.2% (95% CI 66.3–85.0%), 64.6% (95% CI 52.3–74.6%),

TABLE 2 Patient data, disease data, treatment data, and outcomes data for 692 cases of SPN in the National Cancer Database (NCDB)

Variable	NCDB T1-3N0M0 SPN *n* = 599	NCDB malignant SPN *n* = 93	*P*
Patient data			
Patient age in years, median [IQR] (range)	35.0 [26.0–46.0] (18.0–87.0)	44.0 [31.5–60.5] (18.0–66.0)	**< 0.0001**
Male biological sex, *n* (%)	78 (13.0%)	26 (28.0%)	**0.0005**
Race, *n* (%)			0.2637
White	395 (68.5%)	69 (74.2%)	
Black	141 (24.4%)	19 (20.4%)	
Other	32 (5.5%)	2 (2.2%)	
Unknown	9 (1.6%)	3 (3.2%)	
Spanish/Hispanic origin, *n* (%)	116 (19.4%)	32 (26.7%)	0.4900
Insurance status			**0.0028**
Uninsured	36 (6.0%)	8 (8.6%)	
Private insurance	375 (62.6%)	46 (49.5%)	
Medicaid	115 (19.2%)	16 (17.2%)	
Medicare	45 (7.5%)	19 (17.2%)	
Other government	11 (1.8%)	1 (1.1%)	
Unknown	17 (2.8%)	3 (3.2%)	
Comorbid disease, *n* (%)	104 (17.4%)	25 (26.9%)	**0.0283**
Disease data			
Tumor location			**< 0.0001**
Head of pancreas	159 (26.5%)	28 (30.1%)	
Body of pancreas	94 (15.7%)	6 (6.4%)	
Tail of pancreas	259 (43.2%)	29 (31.2%)	
Other	46 (7.7%)	13 (14.0%)	
Unknown	41 (6.8%)	17 (18.3%)	
Tumor size in centimeters, median [IQR]	4.5 [2.9–7.5]	8.0 [4.9–11.9]	**< 0.0001**
Treatment data			
Extent of resection, *n* (%)			**< 0.0001**
Unresected	19 (3.2%)	32 (34.4%)	
Local excision	12 (2.0%)	0 (0.0%)	
Partial pancreatectomy	303 (50.6%)	21 (22.6%)	
Pancreatoduodenectomy	175 (29.2%)	23 (24.7%)	
Total pancreatectomy	52 (8.7%)	8 (8.6%)	
Extended pancreatoduodenectomy	13 (2.2%)	5 (4.5%)	
Unknown	25 (4.2%)	4 (4.3%)	
Nodes examined, *n* (%)*	8.0 [2.0-14.0]	11.0 [6.0–19.0]	**0.0028**
Systemic therapy, *n* (%)	19 (3.0%)	27 (29.0%)	**< 0.0001**
Radiation therapy, *n* (%)	8 (1.7%)	1 (2.1%)	0.1864
Outcomes data			
Post-op LOS in Days, median [IQR]*	6.0 [5.0–8.0]	7.0 [5.0–10.0]	**0.0340**
Follow-up in months, median [IQR]	48.5 [28.3–89.4]	46.2 [6.5–84.7]	**0.0484**
Vital status			**< 0.0001**
Alive	473 (79.0%)	50 (53.8%)	
Dead	19 (3.2%)	32 (34.4%)	
Unknown	107 (17.9%)	11 (11.8%)	

*Resected patients only. *n* number; *IQR* interquartile range; *SPN* solid pseudopapillary neoplasm; *malignant SPN* malignant solid pseudopapillary neoplasm

TABLE 3 Simple and multiple logistic regressions for risk factors associated with malignant SPN (NCDB data)

Variable	Simple logistic regression			Multiple logistic regression		
	OR	95% CI	*P*	OR	95% CI	*P*
Patient age in years (per year)	1.038	1.024–1.052	**< 0.0001**	1.020	0.998–1.043	0.0701
Male patient sex (vs. female)	2.592	1.535–4.286	**0.0003**	1.504	0.600–3.505	0.3610
Private insurance (vs. not)	0.577	0.368–0.904	**0.0159**	0.834	0.435–1.634	0.5886
Pancreatic head tumor (vs. body/tail tumor)	1.776	1.038–3.016	**0.0340**	2.174	1.136–4.166	**0.0186**
Tumor size in centimeters (per centimeter)	1.094	1.045–1.150	**0.0003**	1.154	1.079–1.235	**< 0.0001**

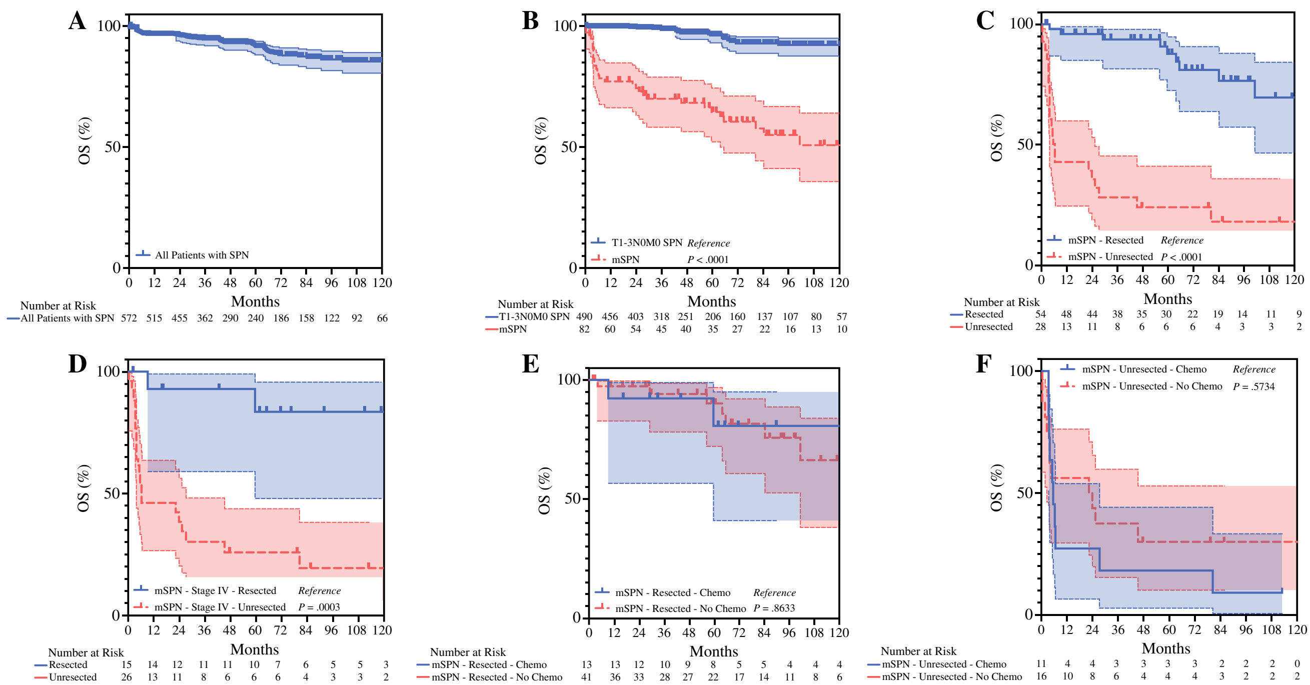

FIG. 3 Overall survival of **A** all patients in the cohort stratified by **B** presence of malignant phenotype, **C** receipt of resection in the setting of malignant phenotype, **D** receipt of resection in the setting of distant metastatic disease, **E** receipt of systemic chemotherapy after resection of malignant SPN, and **F** receipt of systemic chemotherapy for unresected malignant SPN. *mSPN* malignant SPN

and 50.8% (95% CI 35.7–64.0%) versus 99.6% (95% CI 98.0–99.8%), 96.2% (95% CI 93.2–97.8%), and 92.2% (95% CI 87.7–95.1%), respectively. For patients with malignant SPN, resection was associated with significantly improved OS (log-rank $P < 0.0001$; Fig. 3C). Subgroup analysis of patients with stage IV disease, defined as distant metastatic disease, revealed that resection was associated with significantly improved OS (log-rank $P = 0.0001$; Fig. 3D). Among patients with malignant SPN, receipt of systemic chemotherapy was not associated with improved OS whether they did (log-rank $P = 0.8633$; Fig. 3E) or did not undergo resection (log-rank $P = 0.5734$; Fig. 3F).

Within a multivariable Cox proportional hazards regression model adjusting for age, sex, comorbid disease, tumor location within the pancreas, tumor size, and tumor resection, the malignant SPN phenotype was associated with significantly increased hazard of death (HR 3.768; 95% CI 1.524–9.001; $P = 0.0031$; Table 4). Disease resection was associated with significantly decreased hazard of death within the same model (HR 0.087; 95% CI 0.032–0.233; $P < 0.0001$).

DISCUSSION

Given its rarity, predictors of the malignant SPN phenotype and treatment outcomes for these patients are difficult to study. Utilizing orthogonal data analysis, the current study provides evidence supporting resection for malignant SPN and limited efficacy of adjunct nonsurgical therapies for these patients. However, there are several points of consideration when translating these data to clinical practice.

TABLE 4 Univariable and multivariable Cox proportional hazards regression for mortality (NCDB data)

Variable	Univariable Cox regression			Multivariable Cox regression		
	HR	95% CI	*P*	HR	95% CI	*P*
Patient age in years (per year)	1.079	1.061–1.099	**< 0.0001**	1.081	1.050–1.116	**< 0.0001**
Male patient sex (vs. female)	4.396	2.476–7.674	**< 0.0001**	0.493	0.147–1.493	0.2300
Comorbid disease (vs. none)	2.271	1.252–3.988	**0.0052**	1.231	0.418–3.219	0.6849
Pancreatic head tumor (vs. body/tail tumor)	2.449	1.235–4.929	**0.0104**	1.170	0.463–2.904	0.7354
Tumor size in centimeters (per centimeter)	1.040	1.009–1.061	**0.0015**	1.058	1.012–1.093	**0.0024**
Malignant SPN (vs. T1-3N0M0 disease)	10.99	6.278–19.76	**< 0.0001**	3.768	1.524–9.001	**0.0031**
Resected (vs. unresected)	0.038	0.022–0.067	**< 0.0001**	0.087	0.032–0.233	**< 0.0001**

Children with Malignant SPN Demonstrated Superior Disease-Specific Survival Compared with Adults

In the pediatric population, only one disease-specific death was reported.[44] The likelihood of publication bias in this finding is high and mandates external validation.[110] Lee et al. analyzed 62 consecutive pediatric and adult patients with SPN at a single center.[8] Children and adults demonstrated similar rates of malignant features, and there were no tumor-related deaths in their series. Hwang et al. demonstrated 95% disease-free survival and 100% DSS for 45 children with resected SPN, including nine malignant SPN, two of which had distant metastatic disease.[111] Among 228 pancreatic malignancies in children and young adults analyzed within the Surveillance, Epidemiology, and End Results database by Brecht et al., eight patients with "malignant" SPN were identified.[112] The 5-year OS for this cohort was 88%, but cause of death was not available for analysis.[112] Collectively, results of these studies as well as those of the current analysis suggest an indolent behavior of malignant SPN in children. The impact of CSR on DSS for children could not be directly analyzed in this study given that only one child died of disease; however, given the unpredictable natural history of malignant SPN, its relative insensitivity to conventional chemotherapy, and the likelihood of surgeons underreporting individual children who died of their disease, consideration should be given to CSR in children when able to be performed without significant morbidity.

Surgical Resection Improved Survival for Adults with Malignant SPN

Within the current pooled analysis of reported cases, adult patients with malignant SPN who had CSR demonstrated significantly improved DSS. Within the NCDB, patients with malignant SPN, including the subgroup of patients with stage IV disease, had improved OS when they underwent resection. Few data are published comparing resection to observation for malignant SPN, but these data echo previous reports of excellent long term survival for patients with malignant phenotypes who undergo resection.[7,8,12] Notably absent from the current analysis are selection criteria for resection of malignant SPN, which could not be reliably defined. As with other rare cancers, the decision to aggressively resect malignant SPN should be made within the context of a goal-oriented treatment plan that incorporates multidisciplinary expertise and a realistic assessment of surgical candidacy.

Larger Tumor Size and Pancreatic Head Tumor Location Associated with the Malignant SPN Phenotype

Increasing tumor size was found to be independently associated with the malignant SPN phenotype. This is concordant with previously published observations.[12,111,113–115] However, that tumor location in the pancreatic head is associated with malignant SPN has not been previously reported. Hwang et al. reported similar rates of pancreatic head tumors in children with "benign" SPN and malignant SPN.[111] Lee et al. similarly reported no difference in tumor location between "benign" SPN and malignant SPN.[8] The clinical significance of this finding is unclear, as pancreatic head tumor location was not associated with differences in OS after adjusting for patient age, tumor size, malignant phenotype, and resection within the current analysis of the NCDB. More sophisticated radiographic observations have been reported to predict malignant SPN, such as focal capsular discontinuity, although these data are not concordant and warrant further study.[111,116]

Adjuvant Therapies were not Associated with Improved Survival for Patients with Malignant SPN

There are no standardized chemotherapy, radiotherapy, or liver ablation regimens for unresected malignant SPN.[117] Within this orthogonal analysis, the use of systemic chemotherapy failed to demonstrate a survival benefit for patients with malignant SPN, regardless of whether CSR was achieved. Within the pooled analysis, the use of nonsurgical, liver-directed therapies was not associated with a significant difference in DSS. While there are reports of long-term survival among individual patients with unresectable malignant SPN receiving chemotherapy, the inherently slow progression of these tumors makes it hard to appreciate the influence of systemic treatment.[117,118]

Limitations

This study has several limitations that warrant mention. First, the selection criteria for resection of malignant SPN remain undefined and cannot be determined with the current data, introducing an inherent selection bias. The systematic review portion of this analysis is prone to publication bias and limited by its retrospective nature and the nonstandardized reporting of individual cases. Another limitation of the systematic review is the high likelihood that individual cases of malignant SPN within large series of nonmalignant SPN were not captured, as the prespecified search protocol emphasized search terms, such as "malignant" and "metastatic." Within the NCDB, the incidence of malignant SPN was noted to be increasing over time. Whether this is due to increased recognition of extrapancreatic disease or a true increase in the malignant phenotype cannot be determined within the current study, although age-adjusted incidence rates of numerous rare cancers are increasing over time, making this finding plausible.[119] However, as treatments evolve over time, caution must be used when externally applying conclusions from observational analyses with a lengthy study period. Also, information regarding the type or number of cycles of chemotherapy is not captured in the NCDB, and there is no data regarding extent of metastasectomy, disease relapse, or cause of death. Finally, although the NCDB captures the majority of cancer cases in the United States, some cases of SPN may not be captured within either dataset, which limits the extrapolation of the epidemiologic portions of these analyses to the population level.

CONCLUSIONS

Malignant SPN is an uncommon clinical phenotype of a rare pancreatic tumor. The current analysis supports resection of all disease when feasible. Notable findings are that children appear have a more indolent disease course than adults; larger tumors and those located within the pancreatic head have a higher association with malignant SPN; and the use of adjuvant chemotherapy, radiotherapy, and liver-directed therapies were not associated with improved survival. Given the rarity of malignant SPN, prospective, randomized trials are not feasible. Future studies should include multicentered experiences with standardized data collection and detailed histopathological data.

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