Natural History of Preoperative Subcentimeter Pulmonary Nodules in Patients With Resectable Pancreatic Adenocarcinoma

A Retrospective Cohort Study

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Objective: To determine the detection rate, radiologic characteristics, and natural history of incidental subcentimeter pulmonary nodules (SCPN) among patients with resectable pancreatic adenocarcinoma and to clarify whether further preoperative evaluation should be considered.

Background: The clinical significance of SCPN detected by routine preoperative abdominal imaging in patients with pancreatic adenocarcinoma is unknown.

Methods: Patients who underwent resection for pancreatic adenocarcinoma between 2000 and 2010 were queried from a prospectively maintained database at a single institution. Pre- and postoperative computed tomographic (CT) imaging was independently reviewed and the presence and radiologic features of SCPNs were analyzed for associations with overall survival (OS).

Results: Of the 463 patients who met inclusion criteria, 329 (71%) had reviewable preoperative imaging. Preoperative SCPNs were described in 59 patients (18%), and 41 patients had follow-up imaging available for review. Only increasing age (67.1 vs 63.5 years; $P = 0.005$) was associated with the presence of SCPN. Six patients (1.8%) had new or enlarging nodules after surgery, of whom 5 (1.5%) had confirmed metastatic adenocarcinoma. There was no difference in OS between patients with or without preoperative SCPN (16.1 vs 19.1 months; $P = 0.201$). No radiographic criterion of SCPN (including number, size, laterality, calcification, or contour) was associated with OS.

Conclusions: Neither the presence of preoperative SCPN nor nodule characteristics was associated with OS among patients who underwent pancreaticoduodenectomy (PD) for pancreatic cancer. These data do not support routine additional workup of preoperative SCPN in patients with resectable pancreatic adenocarcinoma.

Keywords: lung nodules, outcomes, pancreatic adenocarcinoma, pancreaticoduodenectomy, pulmonary nodules, Whipple

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Pancreatic adenocarcinoma has an overall 5-year survival of approximately 5% and is the fourth leading cause of cancer-related deaths in the United States.[1] Surgical resection offers the only chance for cure in the minority of patients who present with localized, resectable disease. However, the 5-year survival of resected patients is only 20%, highlighting the systemic nature of the disease.[2]

A pancreatic protocol computed tomographic (CT) or magnetic resonance imaging (MRI) scan with 3 phases of imaging and thin cuts (≤3 mm) through the pancreas is the most common staging test used to determine resectability. Optimal multiphase imaging techniques includes noncontrast, arterial, pancreatic parenchymal, and portal venous phases of contrast.[3] Pancreas protocol MRI is also emerging as an alternative to CT for patients. Regardless of modality, these scans invariably include the lung bases and indeterminate subcentimeter pulmonary nodules are not infrequently observed.[4] The clinical significance of these pulmonary nodules is unknown.

Subcentimeter pulmonary nodules detected on preoperative imaging represent a clinical dilemma, because noncalcified nodules can be detected in approximately 25% of healthy subjects in large screening studies.[4–7] However, the presence of metastatic disease or a primary lung cancer may preclude curative resection or alter the course of disease management. To make matters difficult, subcentimeter pulmonary nodules (SCPN) often elude further diagnostic testing by largely falling below the level of detection for positron emission tomographic (PET)-CT scans[8–10] and escaping reliable localization for fine-needle aspiration.[4] In a study of 15,865 adults who underwent a transthoracic needle lung biopsy for a nodule found on CT scan, Wiener et al[11] found that 15% suffered a pneumothorax and 1% experienced bleeding complications. The authors question the overuse of CT scans and lung biopsies because 98% of nodules are found to be benign. Percutaneous lung biopsies for nodules measuring less than 1 cm have been found to be nondiagnostic in approximately 8% to 55%, malignant in 52% to 56.1%, and benign or atypical in 25% to 36%.[2,12–14] The associated morbidities of an invasive diagnostic thoracotomy for pulmonary nodules measuring less than 1 cm are generally considered to outweigh potential diagnostic benefit.[15]

The purpose of this study was to determine the prevalence, radiologic characteristics, and natural history of SCPN detected among patients with resectable pancreatic adenocarcinoma to clarify whether further preoperative evaluation or alternative management should be considered.

METHODS

We retrospectively reviewed a prospectively maintained, institutional review board–approved database of patients undergoing surgery for adenocarcinoma of the head of the pancreas at Barnes-Jewish Hospital, Washington University School of Medicine, St Louis, Missouri. Patients undergoing surgery from 2000 to 2010 were included. This time period was chosen on the basis of availability of archived imaging examinations and to allow for adequate follow-up. Patient records were queried to determine the presence of pulmonary nodules on preoperative or immediate perioperative (<5 days) CT reports of the chest or abdomen. Imaging that was deemed inadequate (eg, poor quality, nonpancreatic protocol) was repeated at our

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institution. All of the patients who underwent pancreatic resection for cancer in this study had high-quality imaging (pancreatic protocol CT or MRI) performed within 30 days of their surgery. A high-quality pancreatic protocol CT or MRI is defined as a study with 2 mm cuts through the upper abdomen and pancreas with a noncontrast, arterial, and portal venous phase. Pre-, peri-, and postoperative data were maintained in the database, including patient demographics and history, laboratory and radiographic data, operative details, pathology reports, and follow-up information. Vital status was determined by the medical record and the social security death index.

Preoperative CT scans with documented pulmonary nodules and corresponding postoperative follow-up scans were reevaluated by a single blinded chest radiologist (C.R.) to document the presence and imaging features of pulmonary nodules, including changes in nodule size and character over time. The presence and imaging features of pulmonary nodules were analyzed for an association with overall survival (OS). A *pulmonary nodule* was defined as malignant if there was an increase in size or number of nodules or a histologic diagnosis of cancer by cell cytology, biopsy, or autopsy. Patients with preoperative pulmonary nodules 10 mm or bigger in size were excluded from analysis.

Radiologic features of pulmonary nodules were evaluated on the bases of number, size, and laterality. Each nodule was also classified by its appearance (solid, calcified, or ground glass) and contour (smooth, lobular, or spiculated).

STATISTICAL ANALYSIS

Comparisons of patient characteristics across different groups were performed using the Fisher exact test or a 2-sided *t* test for categorical or continuous variables, respectively. Logistic regression was utilized to assess the effect of clinical and radiologic covariates on mortality to obtain hazard ratios and *P* values. Overall survival based on all-cause mortality was chosen as the endpoint for analysis. Because calcified nodules are often regarded as benign,[4,15] analyses were performed comparing patients with pulmonary nodules to patients without pulmonary nodules, and a separate analysis was performed comparing patients with noncalcified nodules to patients with calcified or absent pulmonary nodules. Kaplan-Meier survival curves were created to compare the survival differences between patients with and without preoperative pulmonary nodules, between patients with noncalcified pulmonary nodules and the remaining patients, and between patients with enlarging or new pulmonary nodules and the remaining patients. *P* values of less than 0.05 were considered significant. Data was analyzed using SAS [version 9.2, Cary, NC].

RESULTS

A total of 463 patients underwent pancreaticoduodenectomy (PD; Whipple procedure) for adenocarcinoma of the head of the pancreas from 2000 to 2010. Of these, 329 (71%) had reviewable preoperative imaging. Clinical, treatment, and pathologic details are summarized in Tables 1 and 2.

Pulmonary nodules were identified in 69 (21%) of 329 patients. Of these patients, 59 (18%) patients had subcentimeter nodules. Forty-one patients (12.5%) had follow-up CT imaging available for review (Fig. 1). The median number of nodules per patient was 2 and the median size of the largest SCPN was 5 mm. SCPNs were bilateral in 14 patients (4.3%), calcified in 19 patients (5.8%), solid in 31 patients (9.4%), and spiculated in 2 patients (0.6%). Seven patients (11.9%) had pleural-based nodes, none of which were found in isolation. After PD, 6 of 41 patients (17%) were found to have enlarging pulmonary nodules, whereas 35 of 41 patients continued to have stable nodules. None of the patients with pleural-based nodes had enlarging or metastatic nodules on follow-up. Nodules were either outside the field-of-view or the follow-up imaging was unavailable in 26 of 59 cases and no preoperative nodules were identified in 2 of 59 cases where a report indicated the presence of a nodule. Five of the 59 patients (1.5%) were confirmed to have metastatic pancreatic adenocarcinoma in the lung: 4 underwent thoracentesis with cytology positive for malignant cells and 1 patient was found to have pulmonary metastases at autopsy. No subcentimeter pulmonary nodules were biopsied or resected.

The only clinical variable associated with the presence of SCPN on the preoperative CT scan (calcified and noncalcified) was increasing age (67.1 vs 63.5 years; $P = 0.005$) (Tables 1, 2). There was no difference in gender or smoking history between patients with and without SCPN.

TABLE 1. Comparing Clinical and Pathologic Characteristics of Patients With Versus Without Preoperative SCPN

	Patients With Nodules (Calcified and Solid) (N = 59) N (%)	Patients Without Nodules (N = 260) N (%)	*P*
Male gender	31 (53%)	122 (47%)	0.472
Age at surgery	67.1 (±8.3)	63.5 (±10.8)	0.005
Race (Caucasian)	54 (92%)	228 (88%)	0.504
Margin status (free; positive; tumor within 1 mm)	36 (61%); 18 (31%); 5 (8%)	177 (68%); 65 (25%); 18 (7%)	0.558
Smoking history (yes; no; past)	24 (41%); 9 (15%); 26 (44%)	84 (33%); 73 (28%); 103 (40%)	0.099
Smoking in pack years	32.0 (±26.9)	41.7 (±34.9)	0.190
Total Bilirubin (mg/dL)	7.6 (±33.2)	4.8 (±7.5)	0.530
CA19–9	938	814	0.707
Histologic grade (well differentiated; moderately differentiated; poorly differentiated; could not be assessed)	1 (2%); 25 (42%); 32 (54%); 1 (2%)	14 (5%); 112 (44%); 128 (50%); 6 (2%)	0.282
Max tumor diameter (mm)	2.98 (±1.0)	3.05 (±1.4)	0.651
Tumor stage (stage 1; stage 2)	2 (3%); 57 (97%)	26 (10%); 224 (86%)	0.086
+ Chemotherapy	17 (29%)	88 (34%)	0.540
+ Radiation Therapy	37 (63%)	171 (66%)	0.652
Survival (mo)	Median = 12.6	Median = 16.3	0.172

TABLE 2. Comparing Clinical and Pathologic Characteristics of Patients With Noncalcified SCPN Versus Calcified or No SCPN

	Patients With Solid Nodules (N = 41), N (%)	Patients With Calcified Nodules and Without Nodules (N = 278), N (%)	*P*
Male gender	21 (51%)	132 (47%)	0.738
Age at surgery	67.4 (±8.0)	63.6 (±10.7)	0.008
Race (Caucasian)	40 (98%)	242 (87%)	0.063
Margin status (free; positive; tumor within 1 mm)	24 (59%); 14 (34%); 3 (7%)	189 (68%); 69 (25%); 20 (7%)	0.436
Smoking history (yes; no; past)	15 (37%); 7 (17%); 19 (46%)	93 (34%); 75 (27%); 110 (39%)	0.390
Smoking in pack-years	32.9 (±29.4)	41.0 (±34.4)	0.341
Total Bilirubin (mg/dL)	9.5 (±40.1)	4.7 (±7.3)	0.456
CA19–9	985	815	0.717
Histologic grade (well differentiated; moderately differentiated; poorly differentiated; could not be assessed)	1 (2%); 16 (39%); 23 (56%); 1 (2%)	14 (5%); 121 (44%); 137 (49%); 6 (2%)	0.262
Max tumor diameter (mm)	2.91 (±1.07)	3.06 (±1.34)	0.527
Tumor Stage (stage 1; stage 2)	1 (2%); 40 (98%)	27 (10%); 241 (87%)	0.141
+ Chemotherapy	12 (29%)	93 (33%)	0.722
+ Radiation therapy	27 (66%)	181 (65%)	1.00
Survival (mo)	Median = 10.2	Median = 16.3, Median = 65.1	0.116

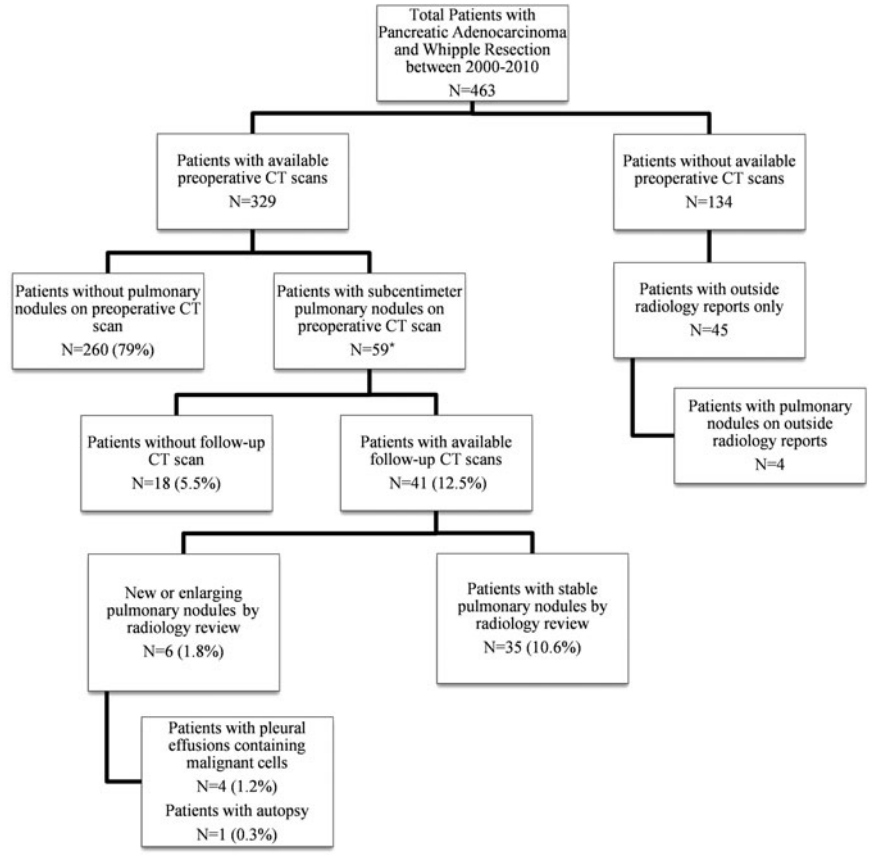

FIGURE 1. New or enlarging pulmonary nodules by radiology review.*Ten patients had pulmonary nodules that were over 1 cm and were excluded from analysis.

Median follow-up after surgery was 16.2 months, and the median OS after surgery for all 329 patients was 20.3 months. There was no difference in OS between patients with or without preoperative subcentimeter pulmonary nodules [16.1 (CI: 9.5–20.6) vs 19.1 (CI: 16.2–22.1) months; $P = 0.201$] (Fig. 2). Similarly, there was no difference in median OS between patients with noncalcified nodules and patients with calcified or absent nodules [15.3 (CI: 8.8–20.6) vs 19.1 (CI: 17.2–22.1) months; $P = 0.309$] (Fig. 3). No radiographic criterion of SCPN including number, size, laterality, calcification, or contour was associated with OS (Table 3).

Among the cohort of 329 patients, the only presenting clinical symptom associated with significantly increased mortality was

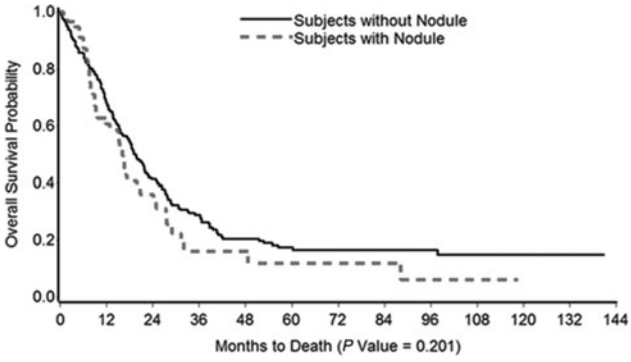

FIGURE 2. Comparing subjects with pulmonary nodules versus subjects without nodules.

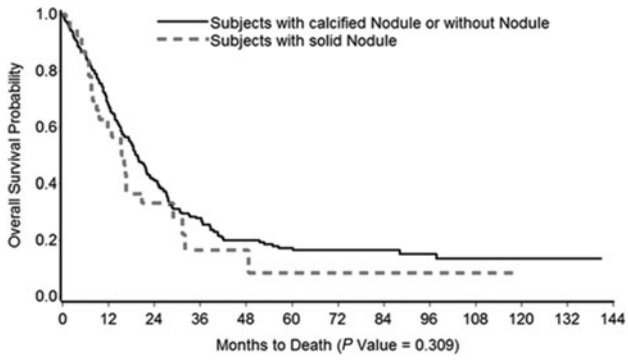

FIGURE 3. Kaplan-Meier curve comparing OS of patients with non-calcified vs calcified or absent SCPN.

jaundice (HR = 1.93, $P = 0.024$). As expected, tumor grade and N stage were significantly associated with mortality (HR = 6.62 and 3.22, $P = 0.032$ and 0.001, respectively). Patients who received perioperative chemotherapy demonstrated improved OS compared with those who did not (HR = 0.402, $P = 0.001$).

TABLE 3. Regression Analysis for Predicting Overall Mortality From Radiologic and Clinical Characteristics

Variable	HR (95% CI)	*P*
Total no. nodules	0.916 (0.628–1.334)	0.646
Size of largest nodule	1.347 (0.965–1.881)	0.080
Bilateral	1.207 (0.321–4.533)	0.780
Calcified	1.029 (0.332–3.186)	0.961
Solid	1.375 (0.457–4.137)	0.571
Ground glass	0.593 (0.119–2.960)	0.523
Spiculated	0.462 (0.027–7.802)	0.592
Smooth	2.235 (0.290–17.219)	0.440
Lobular	No such nodule <1 cm	NA
Radiologist (C.R.) finds nodules worrisome	6.046 (0.241–151.472)	0.273
Presence of calcified or solid nodules	1.119 (0.579–2.164)	0.737
Presence of solid nodules only	1.197 (0.508–2.821)	0.681
Positive smoking history	0.785 (0.015–1.585)	0.679
Symptomatic	1.706 (0.448–6.493)	0.433
Weight loss	1.108 (0.658–1.869)	0.697
Abdominal pain	0.823 (0.490–1.379)	0.459
Jaundice	1.930 (1.089–3.424)	0.024
Pruritus	1.278 (0.769–2.123)	0.342
Nausea	1.053 (0.654–1.694)	0.830
Vomiting	1.170 (0.690–1.98)	0.558
Pack years	1.001 (0.991–1.011)	0.858
Total bilirubin	0.995 (0.980–1.009)	0.474
CA19–9	1.000 (0.999–1.001)	0.065
Vascular resection	1.342 (0.810–2.225)	0.253
Histologic grade	6.622 (1.956–22.42)	0.032
Lymphatic invasion	1.805 (0.263–4.073)	0.474
Venous invasion	1.788 (0.700–4.276)	0.864
Perineural invasion	1.453 (0.901–2.342)	0.236
Margin status	1.264 (0.852–1.676)	0.069
Tumor size	1.045 (0.866–1.261)	0.646
T stage	2.353 (0.136–4.842)	0.380
N stage	3.220 (1.503–6.907)	0.001
Overall stage	2.534 (1.141–5.628)	0.022
Perioperative chemotherapy	0.402 (0.231–0.698)	0.001
Perioperative radiation	0.929 (0.568–1.519)	0.770

DISCUSSION

SCPNs identified on routine CT staging for pancreatic adenocarcinoma are common and their natural history is unknown. Here, we demonstrate that neither the presence of SCPNs nor nodule characteristics is associated with OS in patients undergoing resection for pancreatic cancer. Importantly, confirmed pulmonary metastatic disease in this patient cohort was rare, occurring in only 5 of 329 patients (1.5%). It was also observed that all the pleural-based nodules were found in the presence of other nodules in the lung parenchyma, and that none of them enlarged on follow-up.

Detection of subcentimeter pulmonary nodules will undoubtedly become increasingly common as preoperative imaging techniques become more sophisticated. Current diagnostic limitations preclude satisfactory risk stratification of these nodules, which can complicate treatment decisions regarding major oncologic surgeries with high morbidity and curative intent. A compelling example of this clinical dilemma is SCPNs detected preoperatively in patients undergoing PD for pancreatic adenocarcinoma. No studies to date have investigated the prevalence or natural history of these SCPNs after surgery.

Our study demonstrated that the prevalence of preoperative subcentimeter pulmonary nodules in this specific patient population is 18%, roughly equivalent to those reported in cohorts of patients undergoing endovascular abdominal aortic aneurysm repair,[16] resection of hepatic colorectal cancer metastases,[15,17] and even healthy patients with smoking histories.[5,7,18] A caveat in reporting the prevalence is that it originates from indeterminate pulmonary nodules found on routine standard-of-care *abdominal imaging*. Thus, it is important to note that the true prevalence could not be determined because not all patients had the same type of imaging and some patients had follow-up imaging with dedicated chest CT scans. As observed among patients undergoing resection of hepatic colorectal cancer metastases or initiating treatment for breast cancer, the presence of subcentimeter pulmonary nodules was not associated with OS after surgery or other therapy.[15,17,19]

Among patients who underwent hepatic resection for colorectal cancer metastases, Maithel et al[15] reported a trend toward shorter median progression-free survival in patients with preoperative SCPN compared with patients with no SCPN (12 vs 20 months; $P = 0.242$), but there was no difference in 3-year disease-specific survival (70% vs 83%; $P = 0.46$). Similarly, no radiologic characteristics of SCPN were significantly associated with OS.

Routine preoperative chest CTs for staging of patients with pancreatic cancer have not yet been demonstrated to be clinically useful.[20,21] Because pulmonary metastases are generally considered to be present in more advanced stages of disease, the assertion that an isolated pulmonary metastasis in the setting of otherwise resectable pancreatic adenocarcinoma would be unlikely is further supported by this study. In an autopsy series of 154 patients with pancreatic adenocarcinoma, pulmonary metastases occurred without hepatic metastases in 13 (8.4%) cases.[22] In carefully selected patients with no evidence of other sites of disease, pulmonary metastasectomy has been recently described and associated with increased survival.[23]

Although we did not find an association between SCPN and OS, our study is limited by small numbers that may not be able to detect a true difference. These pulmonary nodules may also reflect predominantly benign processes or metastatic foci with relatively indolent biologic activity. Because the increased malignant potential of pulmonary nodules greater than 1 cm has been well-established,[4,19,24] nodules of this size were excluded from our current analysis. Our study is also limited by the fact that a moderate proportion of patients either did not have imaging available for review or were lost to follow-up. Correlation of imaging findings with pathologic specimens was also lacking in most cases, but reflective of current standard practice and the diagnostic challenges presented by SCPNs as described previously.

Importantly, the prevalence of pulmonary nodules in our patient population must be considered in the context of granulomatous disease from histoplasmosis,[25,26] which is endemic in the Missouri river valley that borders our institution. In a recent series of 1560 patients who underwent resection for pulmonary lesions at our institution, 140 cases (9%) were benign and 65% of these cases demonstrated granulomatous inflammation on pathology.[27] National Comprehensive Cancer Network (NCCN) 2013 guidelines for diagnosis and staging of pancreatic adenocarcinoma continues to recommend specialized pancreatic CT (noncontrast, arterial, pancreatic parenchymal, and portal venous phases in 3 mm or less slice thickness through the abdomen) or MRI. PET/CT scan may be considered after formal pancreatic CT protocol in "high-risk" patients to detect extrapancreatic metastases.[3] Currently, routine chest imaging is not part of the initial workup of pancreatic cancer, but has been suggested. Pappas et al[21] demonstrated that a routine staging chest CT and PET-CT did not contribute additional clinical information in 98% of patients. Nordback et al[20] observed that approximately 13% of patients undergoing staging with a routine CT chest study had solid pulmonary nodules and that all but one of these patients were already considered unresectable by conventional staging methods. The national average charge for a patient to undergo a chest CT with contrast (CPT code 71260) is $1800 (newchoicehealth.com). On the basis of our findings, in a population of patients with known pancreatic adenocarcinoma, 12 chest CT scans ($21,600) would need to be performed to discover 1 patient with a positive metastatic nodule to the lung. Considering the additional cost and burden on the health care system, our data does not support the use of routine chest imaging.

CONCLUSIONS

In summary, SCPN is detected in 18% of patients with pancreatic adenocarcinoma undergoing routine preoperative imaging for PD at rates similar to those found in various other groups of patients with and without a history of malignancy. The preoperative presence and CT features of SCPN do not demonstrate an association with OS after surgery. Therefore, our data do not support routine additional workup of preoperative SCPN in patients with resectable pancreatic adenocarcinoma.

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