

Clinicopathological Factors Associated with Recurrence in Patients Undergoing Resection of Pancreatic Solid Pseudopapillary Neoplasm

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Research

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Abstract

Background: Solid pseudopapillary neoplasm (SPN) is an uncommon pathology with a low-grade malignancy. Surgery is the milestone treatment. Nevertheless, despite appropriate management, some patients present recurrence. Risk factors associated with recurrence are unclear. The objective of this study was to identify the clinicopathological factors associated with recurrence in patients with the diagnosis of SPN treated with pancreatic resection.

Methods: In this retrospective single-center study, medical records of patients treated with pancreatic resection from January 2006 to January 2020 were evaluated. Patients with histological diagnosis of SPN were included. Survival analysis was performed to identify the clinicopathological factors related to recurrence.

Results: A total of 589 patients underwent pancreatectomy and, 74(12.6%) were diagnosed with SPN. Seventy patients (94.6%) were female and 4 were male. The median age was 20 years old and, 49(67%) patients were <28 years. The principal symptom was abdominal pain (n=62)(83.8%). The pancreatic head was the most frequent tumor localization (n=32)(43.2%). Distal pancreatectomy was performed in 33(44.6%) patients, followed by pancreaticoduodenectomy (n=32)(43.2%). The median tumor diameter was 7.9cm and, 24(32%) patients presented tumors ≥ 10 cm. Multivisceral resection was performed in 9(12.2%) patients. Four(5.4%) patients presented lymph node metastasis. R0 resection was achieved in all cases. The overall 90-days postoperative morbidity and mortality were 54% and 1.4%, respectively. The pancreatic fistula was the principal postoperative complication(n=27;36.5%). Six(8%) patients presented recurrence after pancreas resection. Liver metastasis was the most frequent recurrence site(n=5). After a median follow-up of 40.2 months, 9(12%) patients died. Five(6.8%) patients died of disease progression. The 1-3-and-5-year OS was 97.1%,90.2% and 79.9%, respectively. The 1-3-and-5-year RFS was 98.4%,89.9% and 87%, respectively. In the univariate Cox regression analysis, age ≥ 28 years (HR=8.61,95%CI:1.1–73.8), tumor diameter ≥ 10 cm (HR=9.3,95%CI:1.12-79.6), invasion of adjacent organs (HR=7.45,95%CI:1.5–36.9), lymph node metastasis (pN+) (HR=16.8,95%CI:2.96–94.9) and, AJCC(TNM) Stage III (HR=10.1,95%CI:1.2–90.9) were identified as predictors for recurrence.

Conclusions: SPN is more frequently diagnosed in young women with a good overall prognosis after an R0 surgical resection even with disease recurrence. Age ≥ 28 years, larger tumors ≥ 10 cm, invasion of adjacent organs, lymph node metastasis(N+) and, AJCC Stage III were predictors factors of recurrence in resected SPN.

Background

Solid pseudopapillary neoplasm (SPN) of the pancreas, first described by Frantz in 1959(1), is a relatively rare disease that represents 1–3% of all exocrine pancreatic tumors(2, 3). SPN is mostly diagnosed in young women (mean age; 28 years old) and presents a female to male ratio of 9.8/1 (4). The tail of the

pancreas is the most frequent localization and, most patients are symptomatic (5). The pathogenesis of SPN is unclear, mutation of the exon 3 of the beta-catenin gene, FLI-1, DOG1, BCL9L expression, and hormone sensitivity had been studied but conclusive evidence is limited (6–10). In the literature it could be defined as a solid-papillary tumor, solid-cystic acinar tumor, Hamoudi or Frantz tumor, papillary-cystic tumor(11, 12); and, in the WHO classification 2010 (13), this tumor was renamed as SPN and defined as a low-grade malignant neoplasm.

Radical surgery is the principal treatment(14), and; 9–13% of resected SPN presents malignant behavior including local spread and remote organ metastasis (5, 15–18). Studies reported the following factors associated with prognosis: lymphovascular invasion, perineural invasion, distant metastasis, the involvement of surrounding tissue. However, the results remain controversial because of the small number of studies and patients (4, 11). Although some SPN shows malignant compartment, the prognosis of SPN after surgery is generally good with a 5-year overall survival > 95% (19). As such, it is important to identify patients with SPN who have a poor prognosis for tailoring surveillance after surgery. Our study aims to evaluate clinicopathological factors associated with recurrence in patients diagnosed with SPN.

Methods

Study population

Patients who underwent resection of pancreas benign and malignant primary tumors with curative intent at the National Institute of Neoplastic Diseases INEN from January 2006 through January 2020 were identified from a prospectively compiled database. Patients with pathological diagnoses of SPN were included in the study. SPN was diagnosed based on the current WHO classification(20). The study was approved by the institutional review board at the National Institute of Neoplastic Diseases INEN.

Preoperative assessment

Preoperative assessment of the thorax, abdomen, and pelvis was performed using computed tomography with a contrast agent. Magnetic resonance imaging was performed if necessary. A completed blood count, coagulation profile, renal and hepatic function test, tumor markers including Carcinoembryonic antigen (CEA) (< 5 ng/mL) and Carbohydrate antigen 19 – 9 (CA19-9) (< 37 U/mL) were examined. Additionally, nutritional, psychological, and cardiological evaluations were performed. We did not perform a preoperative tumor biopsy.

Surgical Procedure

The surgical procedure was selected based on the tumor localization. Conventional pancreaticoduodenectomy (PD) or pylorus-preserving PD was performed for tumors located in the pancreas head. Two techniques were performed for pancreato-enteric anastomosis (duct-to-mucosa and modified telescopic), depending on the diameter of the pancreatic duct and the pancreas texture. Conventional distal pancreatectomy (with resection of the spleen) or splenic vessel-preserving distal

pancreatectomy were performed for tumors located in the pancreas tail (Fig. 1) (21, 22). For the tumors located at the neck and proximal body of the pancreas, a central pancreatectomy was performed. Multivisceral resection was performed in cases in which the tumor invaded adjacent organs.

Postoperative management

Postoperative complications were classified according to the Clavien-Dindo classification (23). The pancreatic fistula (PF) was defined based on the International Study Group of Pancreatic Fistula (ISGPF) (24). Namely, PF was diagnosed with amylase level in fluid from the abdominal drainage tube > 3 times the upper limit of normal serum amylase level from the third postoperative day. According to the 2016 update of the ISGPF, pancreatic fistula grade A was redefined as a biochemical leak because of the absence of clinical relevance(25). Postpancreatectomy hemorrhage (PPH) was defined according to the International Study Group of Pancreatic Surgery(26). Postoperative morbidity and mortality were defined as complications and mortality which occurred within 90 days after surgery.

Statistical Analysis

Categorical variables were expressed as numbers and percentages and compared using Fisher's exact test or χ^2 test as appropriate. Continuous variables were expressed as median values with interquartile range (IQR) and compared using the non-parametric Mann-Whitney test. An analysis of the receiver operating characteristic curve (ROC curve) was used to obtain the optimal cut-off values for age and tumor diameter. Optimal cut-off values were used for the dichotomization of the variables in the univariate analysis. The optimal cut-off points for age was ≥ 28 years and for tumor diameter was ≥ 10 cm. Each AJCC stage and its relationship with the recurrence were evaluated separately; AJCC Stage III showed a statistically significant relationship with recurrence and was used for the variable dichotomization. Survival curves including overall survival (OS), and recurrence-free survival (RFS) were estimated using the Kaplan-Meier method. Deaths without recurrence were censored for the RFS analysis. A Cox proportional hazards model analysis was performed to identify factors associated with recurrence. The statistical analysis was performed with IBM SPSS version 22.0. Statistical significance was defined as $P \leq 0.05$.

Results

Clinical Characteristics

From January 2006 to January 2020, a total of 589 patients underwent pancreatic resection. Of these, 74 (12.6%) patients including 70 (94.6%) female patient and 4 (5.4%) male patients were diagnosed as SPN. Demographic and clinicopathologic characteristics were shown in Table 1. The median (IQR) age was 20 (18.2) years, and 49 (67%) patients were < 28 years old. The principal symptom was abdominal pain in 62 (83.8%) patients followed by nausea and vomiting (n = 15; 20.3%) and palpable abdominal mass (n = 8; 10.8%). The median (IQR) tumor diameter was 7.9 (5.8) cm, and 50 (68%) patients presented tumors < 10 cm in diameter. Tumor location is as follows: the pancreas head (n = 32; 43.2%), the pancreas tail (n = 26;

35.2%) and the pancreas body (n = 16; 21.6%). The median (IQR) CEA and CA 19 – 9 levels were 1.1 (0.9) ng/mL and 6.9 (9.8) U/mL, respectively. No patients presented metastatic disease at presentation.

Surgical and pathological characteristics

Surgical and histopathological outcomes were shown in Table 2. Of the 74 patients, 33 (44.6%) underwent distal pancreatectomy, 32 (43.2%) underwent pancreaticoduodenectomy and, 9 (12.2%) underwent central pancreatectomy. The median (IQR) operative time was 300 (168) minutes and, the median (IQR) estimated blood loss was 275 (275) mL. Resection of other organs was performed in 9 (12.2%) patients as follows: right hemicolectomy (n = 4), transverse colectomy (n = 2), segmental colonic resection (n = 2) and gastric fundus resection (n = 1). The median (IQR) hospital stay was 12 (7.5) days. Vascular reconstruction was performed because of tumor involvement to the superior mesenteric vein in 3 patients, the superior mesenteric artery in 2 patients, and the splenic vein in one patient. Lymphovascular, perineural invasion, and lymph node metastasis were found in 5 (6.8%), 5 (6.8%), and 4 (5.4%) patients, respectively. According to the AJCC (TNM) Prognostic Groups, 9 (12%) patients were classified as stage I, 63 (85%) as stage II and, 2 (3%) as stage III.

Postoperative outcomes

Postoperative outcomes were summarized in Tables 3 and Supplementary table 1, respectively. Postoperative complications developed in 40 (54%) patients. Pancreatic fistula was the most frequent complication (n = 29; 54%) followed by pancreatitis (n = 9; 17%), abdominal infectious fluid collection (n = 4; 7%) and PPH (n = 3; 6%). Reoperation was performed in 5 patients (6.8%) for hemorrhage (n = 3; 60%), intestinal obstruction (n = 1; 20%) and anastomotic leak (n = 1; 20%). The overall 90-day mortality was found in one (1.4%) patient who developed PPH.

Recurrence, recurrence-free survival, and overall survival

The median follow-up period was 40.2 (0.5–140) months. In our series, 6 (8%) patients developed recurrence after pancreas resection: liver metastasis (n = 5), peritoneal carcinomatosis (n = 2), and the remnant pancreas (n = 1); and 9 (12.2%) patients died. The 1-, 3-, and 5-year RFS was 98.4%, 89.9% and 87%, respectively. The 1-, 3-, and 5-year OS was 97.1%, 90.2% and 79.9%, respectively (Fig. 2). Demographic and pathologic characteristics of patients with recurrence were detailed in Table 4.

Cox proportional hazards model analysis for RFS

In a univariable Cox proportional hazard model analysis, age \geq 28 years (HR = 8.61, 95% CI: 1.1–73.8), tumor diameter \geq 10cm (HR = 9.3, 95% CI: 1.12–79.6), invasion of adjacent organs (HR = 7.45, 95% CI: 1.5–36.9), lymph node metastasis (N+) (HR = 16.8, 95% CI: 2.96–94.9) and, AJCC (TNM) Stage III (HR = 10.1, 95% CI: 1.2–90.9) were associated with risk factors for recurrence in patients (Table 5) (Fig. 3).

Discussion

SPN is a relatively rare disease and generally regarded as a low malignant potential (20). However, because of the rarity, the factors associated with recurrence after curative-intent resection remain unclear (12, 27–29). Our study included 74 patients, the largest series in Latin America, and showed that age \geq 28 years, tumor diameter \geq 10cm, invasion to adjacent organs, lymph node metastasis, and AJCC stage III were associated with recurrence.

In our study, most patients were female (94.6%) and only 4 patients were male. This is in line with previous studies which showed that SPN was predominant in females suggesting a hormonal factor (30, 31). Studies reported that male patients with SPN present an incidence at a higher age and a compromised survival after surgery (14, 32). In our series, the oldest patient was a 68-year-old male; nonetheless, no recurrence was found in male patients.

Studies reported that the mean age at diagnosis of SPN ranges from 25 to 38 years old (2, 5, 33–35). In the present study, the median age at diagnosis of SPN was 20 years old. SPN is generally found with symptoms (28, 35, 36). In our series, 70 (94.6%) patients had symptoms with the most frequent symptom, abdominal pain. At the moment, there is no evidence of a prognostic role of tumor markers in patients with SPN (3, 27, 37). In our study, Ca 19 – 9 levels were higher in patients with recurrence compared to patients without recurrence but no significant difference was observed ($p = 0.21$).

The pancreas tail is the most common location of SPN (4, 16, 18, 33, 35, 38, 39). However, our study showed that the pancreas head was the most frequent location of SPN ($n = 32$; 43.2%) followed by the pancreas tail (26; 35.2%). This is similar to a report in the Chinese population, which showed that 39.8% of SPN were located at the pancreas head in 553 patients (40).

Resection of SPN remains a curative treatment option. Recurrence rates are relatively low, ranging from 1.5–13.7%, according to previous studies, and the liver was the most common recurrence site (4, 5, 15, 16, 28, 39). In the current study, 6 patients (8%) developed recurrence including liver metastases and peritoneal carcinomatosis. Our study showed that age \geq 28 years, tumor diameter \geq 10cm, invasion to adjacent organs, lymph node metastasis, and AJCC stage III were associated with recurrence. Previous studies reported that larger tumors, lymphovascular invasion, perineural invasion, lymph node metastasis, and positive surgical margins were risk factors for recurrence after resection of SPN (3, 4, 15, 19, 41).

The age at diagnosis has been reported as a risk factor for recurrence after resection of SPN; however, it remains unclear whether the young-onset or the old onset is associated with prognosis (28, 42). Irtan et al (28) reported that patients $<$ 13.5 years old were significantly associated with worse disease-free survival than patients \geq 13.5 years old. In contrast, a retrospective study base on the United States National Cancer Database; reported that pediatric patients (\leq 21 years) were significantly associated with better overall survival than adult patients (\geq 22 years) (42).

Serrano et al (41) reported that invasion of adjacent organs increased the risk of recurrence in patients undergoing SPN resection. Estrella et al (4) also reported that the AJCC staging group classification was

significantly associated with recurrence ($p < 0.01$) but no significant difference was observed in AJCC (pT) Stage ($p = 0.71$).

The association of tumor diameter with recurrence after SPN resection has been reported in previous studies. The tumor diameter of 8 cm and 5 cm was a cut-off value to predict recurrence (15, 19). Our study found that tumor diameter ≥ 10 cm was associated with recurrence in terms of the receiver operating characteristic analysis and a Cox proportional hazards model analysis. This may be attributable to the relatively large tumor diameter in our study compared to the tumor diameter in previous studies (4, 14, 15, 39).

Unsurprisingly, lymph node metastasis is a risk factor for recurrence in our study. Gao, et al. reported a systematic review and showed that the presence of lymph node metastasis might increase the risk of postoperative relapses in patients with SPN (19).

Our study should be understood in the context of limitations. First, our study is conducted under the retrospective study design with a relatively small number of patients. Nonetheless, the diagnosis of SPN is rare, and case series are scarce worldwide. Our study is the largest series in Latin America. The functional change after pancreatectomy was not followed because most patients live in remote areas far from our institution.

Conclusions

In conclusion, SPN is frequently diagnosed in young females. The prognosis is good after R0 resection. However, recurrence may develop in some patients. Our study found that age ≥ 28 years, tumors ≥ 10 cm, invasion to adjacent organs, lymph node metastasis and, AJCC Stage III were risk factors of recurrence in patients undergoing SPN resection.

Abbreviations

Solid pseudopapillary neoplasm (SPN); Overall survival (OS); Recurrence-free survival (RFS); Hazard ratio (HR); Confidence interval (CI); American Joint Cancer Association (AJCC); Tumor, nodes, and metastases (TNM); National Institute of Neoplastic Diseases (INEN); World Health Organization (WHO); Carcinoembryonic antigen (CEA); Carbohydrate antigen 19 – 9 (CA19-9); Pancreaticoduodenectomy (PD) Pancreatic fistula (PF); International Study Group of Pancreatic Fistula (ISGPF); Postpancreatectomy hemorrhage (PPH); Interquartile range (IQR).

Declarations

Ethics approval and consent to participate

The present article was evaluated and accepted by the Ethics Committee of the National Institute of Neoplastic Diseases INEN, Lima, Peru. Also, it complies with current regulations on bioethical research

and was performed following the Ethical Principles for Medical Research Involving Human Subjects, as outlined in The Declarations of Helsinki. The authors declare that this article does not contain personal information that allows identifying patients enrolled.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KP, CLV and FB designed the work. OP, IC and YK analyzed and interpreted the data. OP, YK and EP wrote the paper. EP, ER, JC and FB approved the submitted version.

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Tables

Due to technical limitations, table 1 to 5 is only available as a download in the Supplemental Files section.

Figures



Figure 1

Solid Pseudopapillary Neoplasm. Surgical Specimen (distal pancreatectomy): large round well-defined tumor located in the pancreas tail.

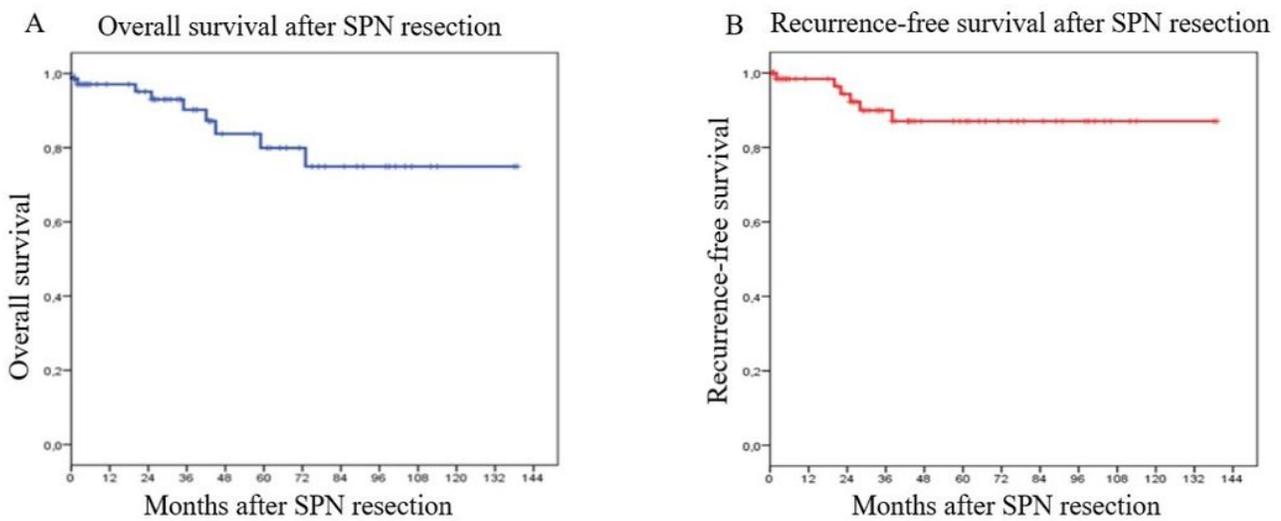


Figure 2

Overall survival (A) and Recurrence-free survival (B) of patients with Solid Pseudopapillary Neoplasm (SPN) who underwent pancreas resection.

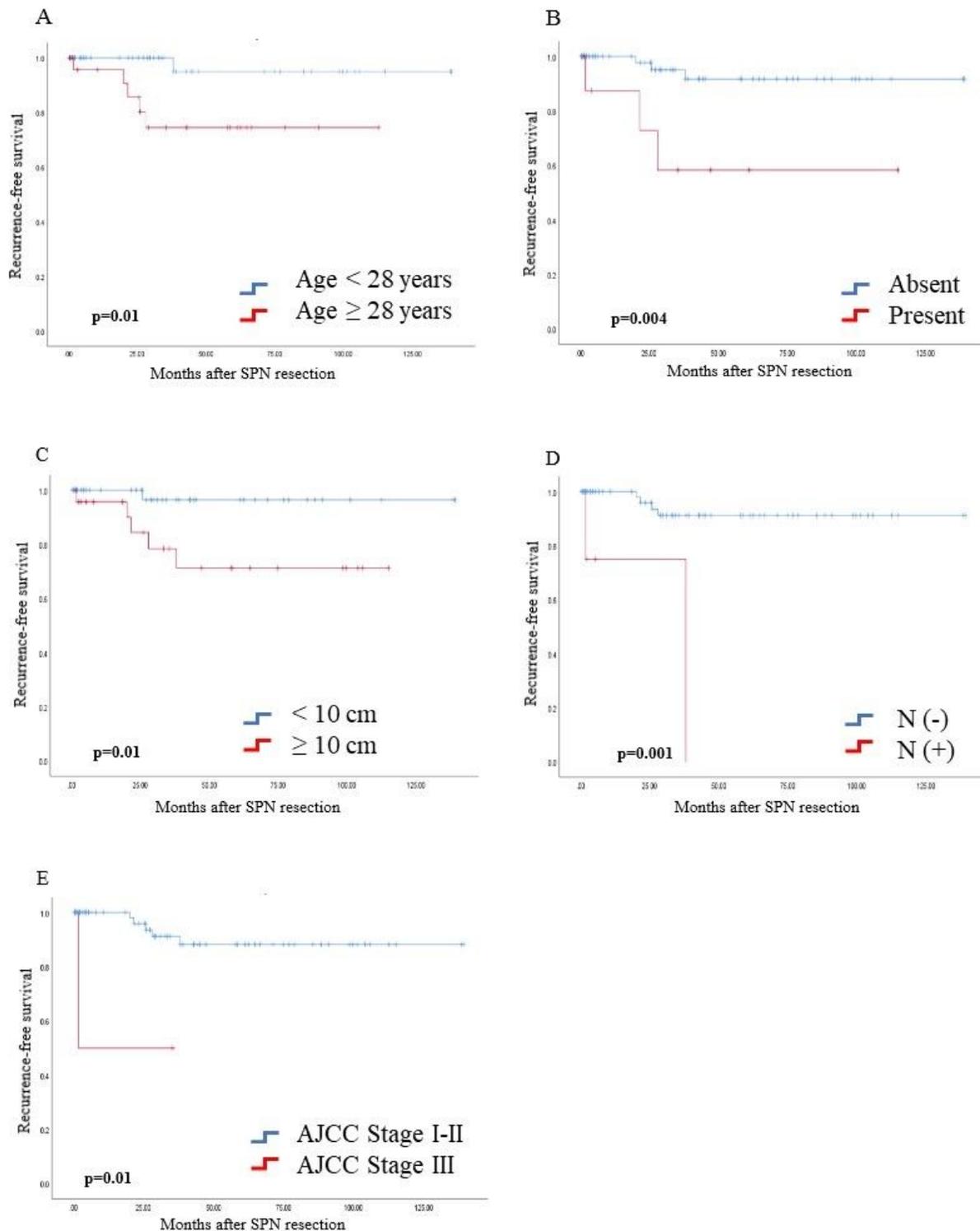


Figure 3

Kaplan-Meier curves of Recurrence-free survival in patients with SPN comparing: (A) patients < 28 years vs ≥ 28 years old; (B) Invasion of adjacent organs Absent vs Present; (C) Tumor diameter < 10cm vs ≥ 10cm; (D) Lymph node metastasis N (-) vs N (+); (E) AJCC Stage I-II vs AJCC Stage III.

Supplementary Files

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