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Title	Laparoscopic distal pancreatectomy for multiple pancreatic solid pseudopapillary neoplasms with marked calcification in a middle-aged female
Author(s)	Sakamoto, Yuzuru; Aimon, Eriko; Takishin, Yunosuke et al.
Citation	Clinical journal of gastroenterology, 18(4), 727-733 https://doi.org/10.1007/s12328-025-02152-9
Issue Date	2025-05-26
Doc URL	https://hdl.handle.net/2115/97863
Rights	This version of the article has been accepted for publication, after peer review (when applicable) and is subject to Springer Nature' s AM terms of use, but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: http://dx.doi.org/10.1007/s12328-025-02152-9
Type	journal article
File Information	huscap_Manuscript_Lap-DP for multiple SPNs_CJG 2025.pdf



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Abstract

Solid pseudopapillary neoplasm (SPN) of the pancreas is a rare, low-grade malignant tumor that primarily affects young females. Multiple SPNs, particularly in older females, are extremely rare. While these tumors generally have a good prognosis, some may progress to malignancy. A 66-year-old female presented with back pain, and CT revealed two calcified masses in the pancreas. The tumor marker levels were normal, and contrast-enhanced CT, ultrasound, and MRI findings suggested multiple SPNs. Owing to significant calcification, preoperative biopsy was not feasible, so laparoscopic distal pancreatectomy (LDP) was performed for diagnosis and treatment. Histopathological examination revealed tumor cells with a round morphology, which were arranged in nested formations, along with areas of calcification on H&E staining. Immunohistochemical analysis revealed positive staining for CD56, vimentin, and β -catenin, whereas bcl-10 was negative, supporting the definitive diagnosis of multiple SPNs. Although SPNs generally have a good prognosis, recurrence is possible, emphasizing the need for complete resection and long-term follow up. Even when preoperative biopsy is difficult due to calcification, aggressive surgical resection is crucial for long-term successful prognosis. Furthermore, LDP offers advantages over traditional open surgery, such as reduced blood loss and faster recovery, and may be considered for diagnosis and treatment in such cases.

45 **Key words:**

46 solid pseudopapillary neoplasms • multiple • pancreas • old female • laparoscopic distal pancreatectomy

47

48 **Abbreviations:**

49 CD56, cluster of differentiation 56; CT, computed tomography; EUS-FNA, endoscopic ultrasound-guided

50 fine needle aspiration; MRI, magnetic resonance imaging; H&E staining, hematoxylin and eosin staining;

51 HBsAg, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody; LDP, laparoscopic distal

52 pancreatectomy; SPN, solid pseudopapillary neoplasm.

Text

Introduction:

Solid pseudopapillary neoplasm (SPN) of the pancreas is a relatively rare disease that occurs most frequently in the body and tail of the pancreas in young females [1, 2]. Moreover, almost all pancreatic SPNs occur singly and in young females, so multiple pancreatic SPNs in old females are extremely rare [2, 3]. SPNs are low-grade malignant tumors, and complete surgical resection is expected to result in a good prognosis [4, 5]; however, in some cases, they can transform into highly malignant tumors and result in a poor prognosis [6]. Here, we report a rare case of multiple pancreatic SPNs with marked calcification in a middle-aged female in which laparoscopic distal pancreatectomy (LDP) was performed successfully and safely for diagnosis and treatment.

Case Report:

A 66-year-old female patient was admitted to a previous clinic complaining of back pain and a plane computed tomography (CT) scan revealed a mass in the tail of the pancreas; thus, she was referred to our hospital. Laboratory data revealed that her blood chemistry, including tumor markers, was normal (Table 1), but a dynamic contrast-enhanced abdominal CT scan revealed two low-density masses measuring 3.2 cm and 1.0 cm in diameter at the tail and body of the pancreas, respectively, with marked calcification (Fig.

1a-d). Abdominal contrast-enhanced ultrasound revealed that the pancreatic tail mass had a clear border, significantly calcified rim, solid and heterogeneous interiors containing cystic structures, and poor blood flow (Fig. 2a, b), though the lesion of the pancreatic body was so small and could not be detected. Magnetic resonance imaging (MRI) revealed that the pancreatic tail mass was heterogeneously hypointense in T1-weighted imaging (Fig. 3a), had relatively high-intensity area with hypointense rim on T2- and diffusion-weighted imaging (Fig. 3b, c), and the pancreatic body mass was relatively low-intensity on each phase (Fig. 3d-f); thus, we finally diagnosed the multiple pancreatic SPNs with marked calcification from the imaging findings. Because the marked calcification around the tumors made endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) difficult, we performed LDP for diagnosis and treatment after consulting with the patient (Fig. 4). Postoperatively, the patient had a pancreatic fistula (Grade B), but it improved with conservative treatment, and she was discharged 43 days after surgery. The resected specimen revealed that the tumors (2.5 cm and 1.2 cm) were located at the tail and body of the pancreas, respectively (Fig. 5a), and the cut surfaces of the tumors were also cystic components with surrounding calcification (Fig. 5b). Tumor cells with a round morphology were arranged in nested formations, along with areas of calcification on H&E staining (Fig. 6a, f). Immunohistochemical findings of pancreatic tail mass indicated that CD56, vimentin, and β -catenin were positive and that bcl-10 was negative (Fig. 6b-e), so the final diagnosis was multiple SPNs of the pancreas. The patient had intensive follow-up appointments without any recurrence.

Discussion:

Pancreatic SPNs are relatively rare pancreatic tumors that were first reported by Frantz in 1959 [7], accounting for 0.2–2.7% of all pancreatic tumors [1], but the number of reported cases has been increasing in recent years due to advances in diagnostic imaging, especially also in males in Japan [3]. The tumor is characterized by a solid structure with a thick fibrous capsule, which expands and grows outside the pancreas and often contains cystic components due to repeated bleeding and necrosis. With respect to the imaging findings of SPNs, cystic components have been reported in 96% of cases, and calcification is observed in 30–50% of cases; thus, pancreatic tumors that contain cystic components or calcification and show gradually increasing staining in the solid part on contrast-enhanced CT can be considered in the differential diagnosis of SPNs [8]. However, these tumors can be difficult to distinguish from other pancreatic tumors, such as neuroendocrine tumors or acinar cell carcinomas, by imaging findings alone. The presence of obstructive jaundice may be helpful in differentiating from pancreatic carcinomas [9], but in such cases, EUS-FNA has a high accuracy rate of 75–100%, making it useful for preoperative diagnosis [10, 11]. However, there are several risks associated with EUS-FNA, such as tumor bleeding, rupture, or spreading of tumor cells, so it is necessary to consider the indications for this procedure [12]. The frequency of multiple SPN cases is approximately 2.1% [3], and Nakamura et al. summarized the cases of multiple SPNs in detail [13]. Among patients with multiple SPNs, almost all were females (90.9%), all had two tumors, the diameters of the tumors were relatively large (median 85 mm), and the tumor locations in the

pancreas or the surgical procedures performed varied. Our case is consistent with the presence of two tumors in the pancreatic tail and body in a female, but the size of both tumors was relatively small, and there was marked calcification compared with previous reports. Because of this difference in clinical features, sex hormones may play a role. SPNs express estrogen and progesterone receptors [14], and estrogen may affect the proliferation of SPNs in vitro [15]. It is expected that tumors grow because they produce large amounts of estrogen and progesterone in young females, but in older females or males, tumors may cause less hemorrhage or necrosis within the tumor leading to lower levels of sex hormones; therefore, these tumors tend to not grow and be smaller and significant calcification. To support this hypothesis, some reports have shown that SPNs in older females or males are smaller than those in younger females [5, 16]. In our case, while the tumor's onset and duration remain unclear, there are no previous reports describing characteristic imaging findings that predict the onset or duration of SPN. If these tumors had developed during youth and grown slowly over time, they would likely have reached a large size; therefore, it is plausible that this case represents de novo, late-onset SPNs in an elderly patient. However, there was no significant difference in age, gender, or calcification when comparing benign and malignant SPNs, although differences in tumor capsule completeness and Ki-67 levels have been observed [5, 16]. Further studies are needed to explore the influence of age or hormonal factors on SPN growth and malignant potential.

SPNs are defined as low-grade malignant tumors [4], so the prognosis is relatively good, and the 10-year

survival rate is 96% [17]. For long-term prognosis, performing complete resection and appropriate surgical procedures is important [5]. Because SPNs can occur anywhere in the pancreas, the surgical procedure must be determined on the basis of the location or size of the tumor, as well as its extent to which it has spread to surrounding organs [18]. Recently, studies on the usefulness of laparoscopic surgery or preserving the pancreatic parenchyma as much as possible have increased [9, 19-22]. We previously reported the usefulness of laparoscopic resection for rare tumors [23], LDP, in particular, decreased blood loss and morbidity, and promoted early recovery and shorter hospital stays than conventional open surgery [24], and Yamaguchi et al. reported the first case of LDP for multicentric pancreatic SPNs [25]. On the other hand, laparoscopic surgery has possibility of port site recurrence or conversion to open surgery, and some reports that reduced surgery increases the risk of postoperative recurrence [26] or complications such as pancreatic fistula have also been published [9]. We also chose LDP at this time, because of its advantages, low-grade malignancy, the small size of the tumors, and the lack of invasion into surrounding organs, but the indications for LDP should be carefully selected.

As mentioned above, complete surgical resection is the most effective treatment for pancreatic SPNs, but there are sometimes disease recurrences (approximately 10–15%) or unresectable cases [5, 27-30]. The factors leading to recurrence, metastasis, and poor prognosis in SPN patients are unclear. Some studies suggested that the pathological characteristics such as a solid/diffuse growth pattern with extensive tumor necrosis, pancreatic parenchymal or capsular invasion, nodal metastasis, and high Ki-67 index are

associated with tumor aggression [17, 31-33]. Common sites of metastasis include the liver, lymph nodes, mesentery, omentum, and peritoneum, with a mean recurrence time of 50.5 months following surgical resection [1]. In previous studies, follow-up CT scans were typically performed every 6-12 months, although some recurrences have been reported as late as 10 years postoperatively [34]. Consequently, patients at risk of recurrence, particularly those with pathologically malignant potential, may require CT imaging every 6 months and vigilant monitoring for 10 years or longer after surgery. Although no standard alternative treatment options, such as chemotherapy or radiotherapy, have been established for recurrent or unresectable cases, systemic chemotherapy with gemcitabine, oxaliplatin, or FOLFOX [35, 36]; tyrosine kinase inhibitors [37, 38]; and most notably, endocrine therapy with tamoxifen [39] has been reported, so these methods may be helpful in the future. Early detection, diagnosis and appropriate treatment for pancreatic SPNs are very important.

This report presents an extremely rare case of multiple pancreatic SPNs in a middle-aged female and the second case in which LDP was performed for the successful and safe diagnosis and treatment of multiple SPNs. Even when preoperative biopsy is impossible due to marked calcification, it is important to aggressively and completely resect pancreatic SPNs for long-term successful prognosis.

Disclosures

Conflict of interest: The authors declare that they have no conflicts of interest.

Ethics approval and consent to participate: Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. Ethical approval was not required for this study as per local or national guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from the patient.

Funding: No funding to declare.

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Table and Figure Legends:

Table 1. Patient laboratory data

WBC, white blood cell; Neut, neutrophil; RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; Plt, platelet count; PT, prothrombin time; APTT, activated partial thromboplastin time; TP, total protein; Alb, serum albumin; T-bil, total bilirubin; D-bil, direct bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ -GTP, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; HBsAg, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Fig. 1a–d Dynamic contrast-enhanced CT findings

A low-density mass measuring 3.2 cm in diameter was located at the tail of the pancreas in axial (a) (white arrowhead) and coronal (b) (white arrowhead) sections. Another low-density mass measuring 1.0 cm in diameter was located at the body of the pancreas in the axial section (c) (black arrowhead) and the coronal section (d) (black arrowhead).

Fig. 2a, b Contrast-enhanced ultrasound examination findings

The pancreatic tail mass had a clear border, significantly calcified rim (a) (white arrowhead), solid and

heterogeneous interiors (a) (black arrowhead) containing cystic structures (b) (white arrowhead), and poor blood flow (b) (black arrowhead). The lesion of the pancreatic body was so small and could not be detected.

Fig. 3a-f MRI findings

The pancreatic tail mass was heterogeneously hypointense in T1-weighted image (T1WI) (a) (white arrowhead). This lesion showed relatively high signal intensity area with hypointense rim in T2-weighted image (T2WI) (b) (white arrowhead) and on diffusion-weighted image (DWI) (c) (white arrowhead). The pancreatic body mass was hypointense in T1WI (d) (yellow arrowhead). This lesion showed relatively low signal intensity area in T2WI (e) (yellow arrowhead), on DWI (f) (yellow arrowhead).

Fig. 4 Intraoperative image

The white mass protruded from the surface of the tail of the pancreas (white arrowhead).

Fig. 5a, b Resected samples

The pancreatic tail tumor (2.5 cm) (white arrowhead) and the pancreatic body tumor (1.2 cm) (black arrowhead) were present (a). The cut surfaces of the tumors were also contained cystic components with surrounding calcification (b) (white and black arrowheads).

Fig. 6a-f Histopathological examination

Tumor cell at pancreatic tail (**a**) and pancreatic body (**f**) with a round morphology were arranged in nested formations, along with areas of calcification on H&E staining. [hematoxylin and eosin (H&E) stain, x400]. Immunohistochemical findings of pancreatic tail mass revealed that CD56 (**b**) [CK56, x400], vimentin (**c**) [Vimentin, x400], and β -catenin (**d**) [β -catenin, x400] were positive in the tumor region, whereas bcl-10 (**e**) [bcl-10, x400] was negative.

Table 1. Patient laboratory data

Peripheral blood counts		Biochemistry		Serology	
WBC	5,000 / μ L	TP	6.7 g/dL	CRP	< 0.02 mg/dL
Neut	57.3 %	Alb	4.2 g/dL	HBsAg	(-)
RBC	433 x 10 ⁴ / μ L	T-bil	0.5 mg/dL	HCVAb	(-)
Hb	13.1 g/dL	D-bil	0.1 mg/dL	Tumor marker	
Hct	39.7 %	AST	21 U/I	CEA	2.6 ng/mL
Plt	24.2 x 10 ⁴ / μ L	ALT	19 U/I	CA19-9	< 1.0 U/mL
Coagulation		ALP	71 U/I		
PT	13.4 sec	γ -GTP	40 U/I		
APTT	30.6 sec	BUN	15.2 mg/dL		
Fibrinogen	216 mg/dL	Cr	0.68 mg/dL		

WBC, white blood cell; Neut, neutrophil; RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; Plt, platelet count; PT, prothrombin time; APTT, activated partial thromboplastin time; TP, total protein; Alb, serum albumin; T-bil, total bilirubin; D-bil, direct bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ -GTP, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; HBsAg, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Figure. 1



Figure. 2

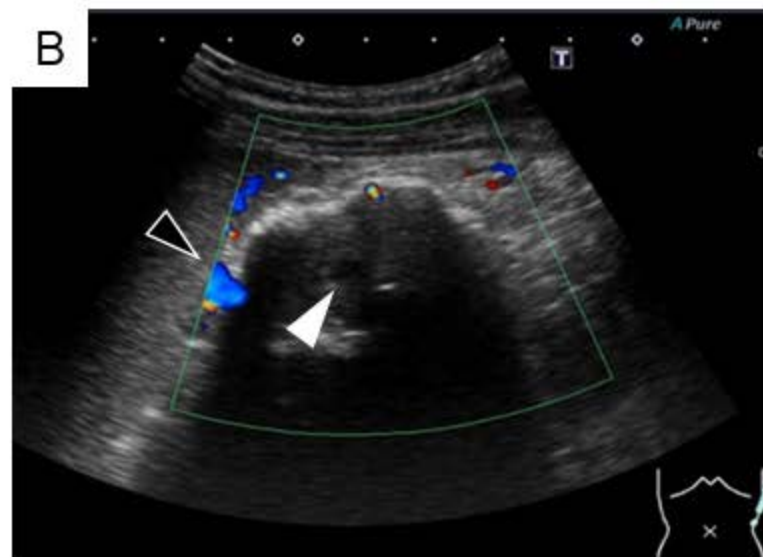


Figure. 3

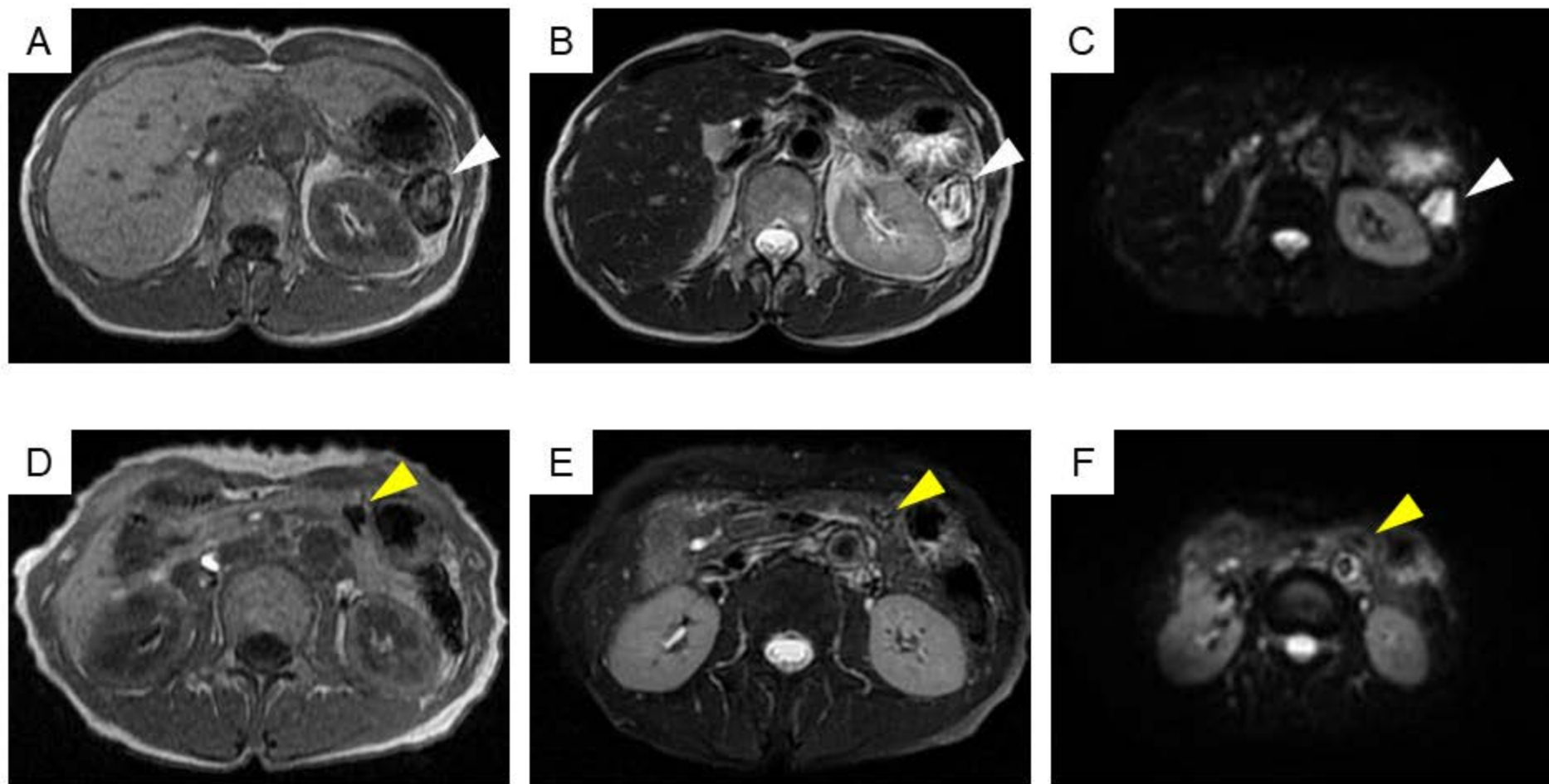


Figure. 4



Figure. 5

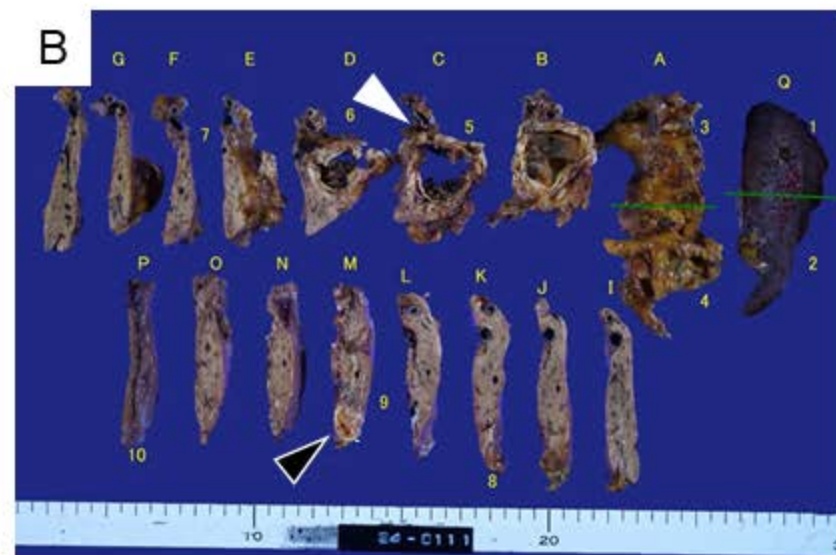
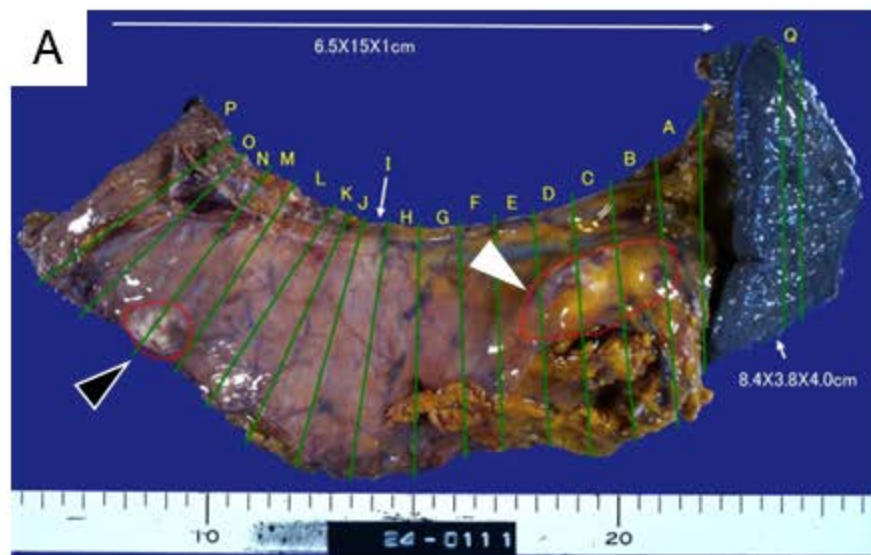


Figure. 6

