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Total pancreatectomy for pancreatic remnant carcinoma five years after pancreaticoduodenectomy: Report a case

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ABSTRACT

INTRODUCTION AND IMPORTANCE: The prognosis of non-invasive intraductal papillary mucinous neoplasma (IPMN) is better than that of pancreatic cancer. However, if the first surgical finding revealed an invasive IPMC, the risk of recurrence was found to be 7–21%.
CASE PRESENTATION: A 76-year-old Japanese man had undergone subtotal stomach-preserving pancreaticoduodenectomy for intraductal papillary mucinous carcinoma non-invasive type at our hospital. No signs of adenocarcinoma at the resection margin were found by pathological examination of frozen sections. Five years later, a blood analysis showed increased serum CA19-9 level. A contrast-enhanced computed tomography scan of the abdomen revealed a mass adjacent to the pancreaticogastrostomy anastomosis. The patient underwent a total pancreatectomy. The tumor was identified as a recurrent IPMC with subserosal invasion, but without nodal involvement. The resection margins were negative. The patient's postoperative course was uneventful, and he was discharged after 12 days. He is being followed up without adjuvant chemotherapy.
DISCUSSION: The prognosis of IPMN is better than that of pancreatic cancer. However the risk of recurrence in invasive IPMC was found to be 7–21%. Therefore, IPMC must be surveilled every three months using tumor markers and imaging. Local recurrence in remnant pancreas is usually treated with systemic therapy. The median long-term survival after total pancreatectomy (range 7–24 months) was shown to be better than when chemotherapy alone was used (range 10–13 months).
CONCLUSION: We chose secondary surgery in term of survival time although there are quality of life drawbacks that currently make total pancreatectomy more inappropriate in patients than chemotherapy.

1. Introduction

Intraductal papillary mucinous neoplasms (IPMNs) are mucin-producing cystic pancreatic lesions, precursors to pancreatic ductal adenocarcinoma (PDAC), and classified as low-grade dysplasia (LGD), high-grade dysplasia (HGD), and invasive intraductal papillary carcinoma (IPMC) [1]. There are three IPMN groups (without carcinoma in situs (CIS) invasion, slight CIS invasion, and massive IPMN-derived invasive carcinoma) with four histological types (hyperplasia, adenoma, adenocarcinoma, and invasive cancer). After primary resection in patients with non-invasive lesions and slightly invasive lesions, the survival rate was 73.2%–100%, whereas it was 34%–62% in patients with invasive carcinoma [2]. Although the prognosis is better for of non-invasive and slightly invasive IPMC than for ordinary-type pancreatic cancer, there is still a possibility of local recurrence with multi-centric occurrence in the remnant pancreas. For non-invasive or slightly invasive IPMC, the reported overall disease recurrence rate is 1.3%–9.3%, with a pancreatic remnant recurrence rate of 1.3%–6.3% [3,4]. The recurrence time ranges from 6 months or less than 11 years after the primary resection. Herein, we report a case of total pancreatectomy for remnant pancreatic carcinoma after subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) for IPMC five years prior. The work is reported in line with the SCARE 2020 Guidelines [5].

2. Presentation of case

A 76-year-old Japanese man visited our department by referral from nearby hospital for an upper abdominal discomfort examination. Contrast-enhanced computed tomography (CT) showed that the main pancreatic duct was dilated by 10 mm, but there were no nodules in the pancreas, and there was no indication of metas-

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tasis to the lymph nodes, liver, or lung. On admission, laboratory testing did not indicate liver or kidney dysfunction, and the remaining hematologic parameters were within normal ranges (including serum carcinoembryonic antigen (CEA) [1.7 ng/dL] and carbohydrate antigen 19-9 (CA19-9) levels [9.0U/mL]). IPMC or main duct IPMN was suspected, and the patient was scheduled for SSPPD with lymph node dissection. The operation was performed by our team, which consisted of surgeons performing 30 operations a year in the hepatobiliary and pancreatic field. The total operating time was 530 min, and the intraoperative blood loss was 290 mL.

The specimen was 10.0 cm(l)×3.0 cm(w)×1.8 cm(h),IPMC[pTis, INFa,ly0,v0,ne0, pN0(0/12),pPM0.pDM0,pRM0,M0,pStage0], and there was no exposure to the peeled surface. Pathological examination of the frozen sections showed no signs of adenocarcinoma at the resection margins (Fig. 1). Hematoxylin and eosin staining showed that the main pancreatic duct was dilated by mucous retention and that a papillary tumor grew inside the duct. Atypical cells with chromatin and an irregular nuclear-to-cytoplasmic ratio were observed in the pancreatic duct (Fig. 2a, b). Morphological and immunohistochemical analyses showed that the cells were positive for the genes CDX2, MUC2, MUC5AC, and MUC6, and negative for MUC1. Furthermore, immunohistochemical analyses showed that the cells were Ki-67 positive, and there was no p53 overexpression (Fig. 2c–i). This specimen was diagnosed as IPMC non-invasive type with an intestinal epithelial subtype based on the pathological findings. The patients suffered delayed gastric emptying twice, whereas

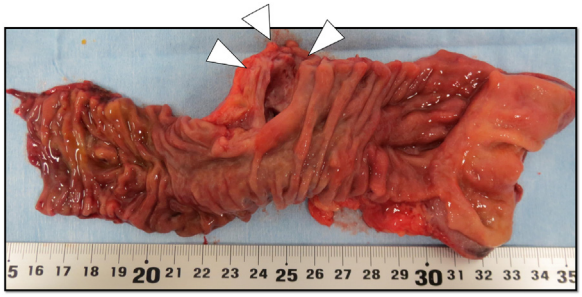

Fig. 1. Macroscopic findings. The specimen was 10.0 cm × 3.0 cm × 1.8 cm, intraductal papillary mucinous carcinoma (IPMC; pTisN0M0, pStage0), and there was no exposure to the peeled surface. No signs of adenocarcinoma at the resection margin were found by pathological examination of frozen sections.

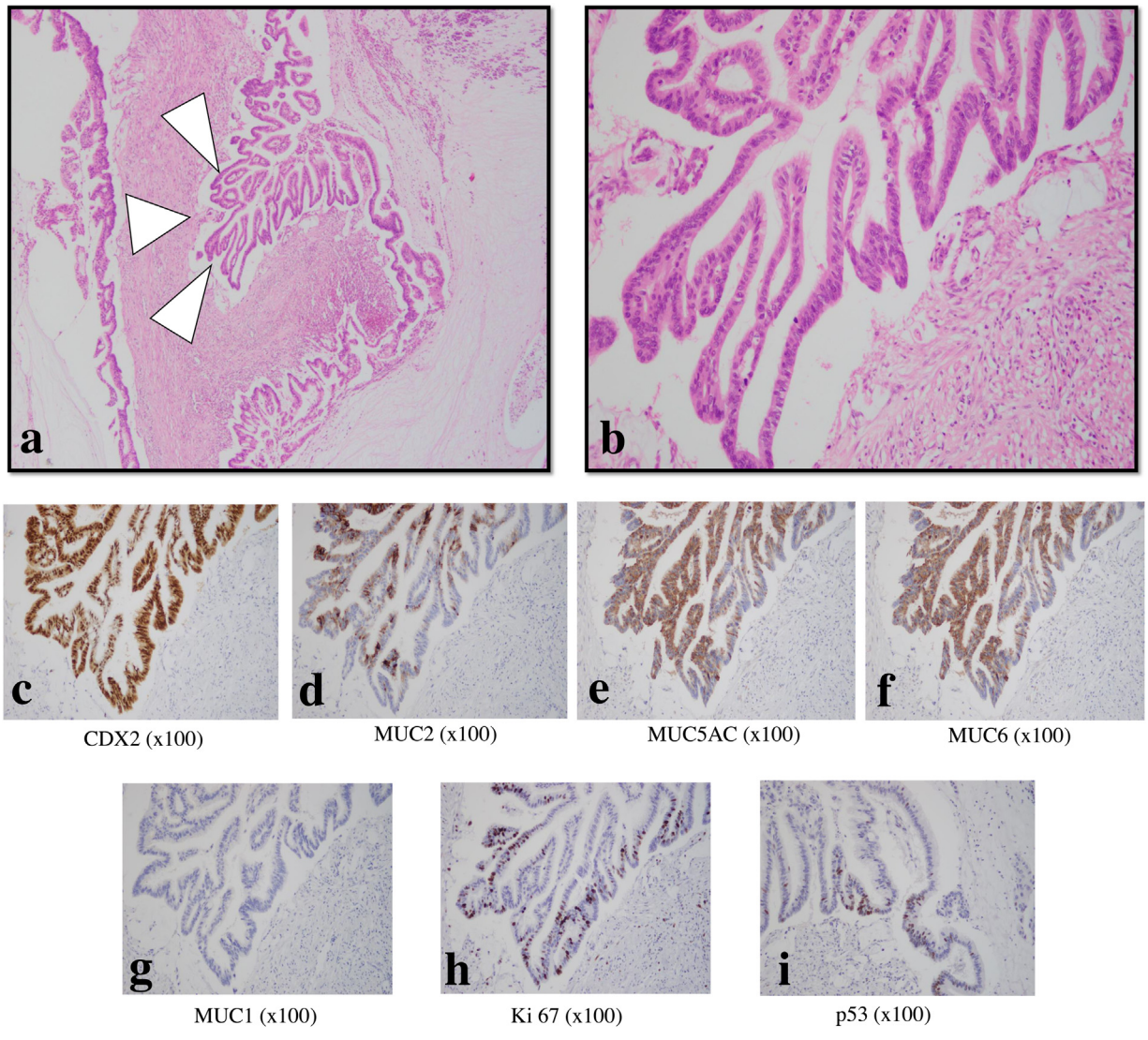

Fig. 2. Microscopic, morphological, and immunohistochemical findings.
(a) (b) In hematoxylin and eosin stain, these specimen were observed that the main pancreatic duct was dilated by mucous retention, and papillary tumor was increased in duct. Atypical cells with chromatin and irregular nuclear-to-cytoplasmic ratio was observed in pancreatic duct.
(c)(d)(e)(f)(g)(h)(i) Immunohistochemical analyses showed that the cells were positive for CDX2, MUC2,MUC5AC and, MUC6 and negative for MUC. Besides, immunohistochemical analyses showed that the cells were positive for Ki 67, and there was no overexpression for p53.

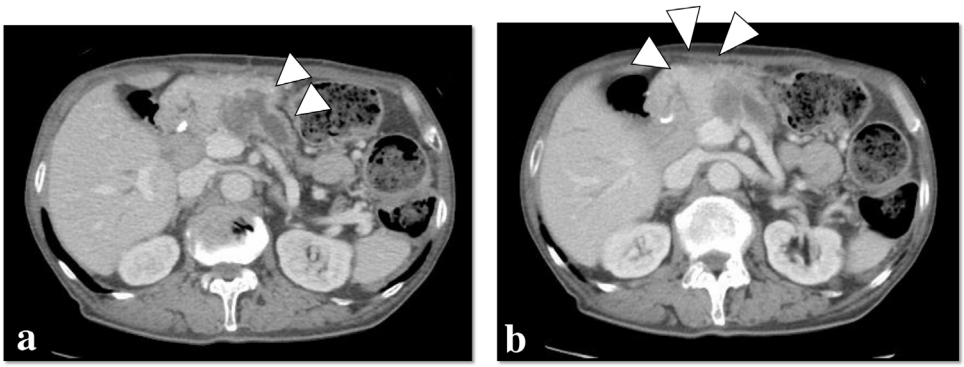

Fig. 3. Abdominal contrast-enhanced computed tomography scan.
(a) (b) A follow-up Contrast-enhanced CT scan revealed a mass adjacent to pancreaticogastrostomy anastomosis (white arrows), no nodules were found in remnant pancreas, and there was no indication of metastasis to the lymph nodes, liver, and lung.

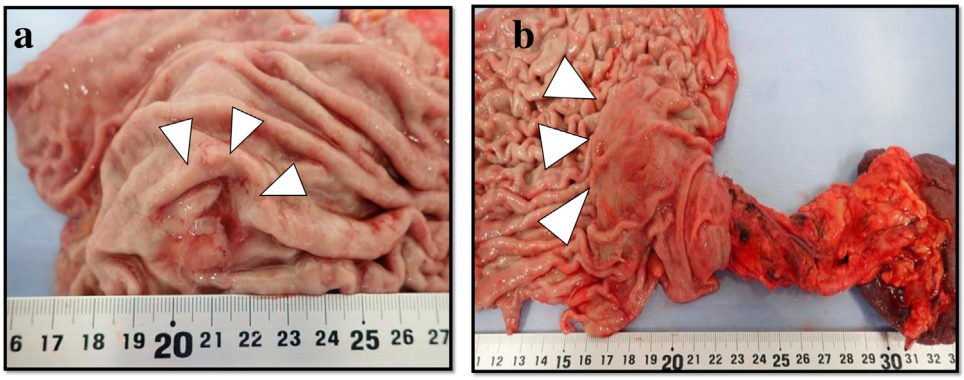

Fig. 4. Macroscopic findings. The tumor was identified as a recurrent IPMC with subserosal invasion, but without nodal involvement (pT3N0M0; pStageIII).The resection margins were negative.

this condition was improved by the conservative therapy, and he was discharged after 54 days. The patient continued routine follow-up examinations (e.g.,ultrasonography and dynamic CT) every six months without adjuvant chemotherapy as per the pathological findings.

The patient was not oncologically suffered recurrence and metastasis for five years after initial surgery. However, CEA and CA19-9 levels (11.5 ng/mL and 30.3U/mL, respectively) and glucose tolerance worsened. A follow-up CT scan revealed a mass adjacent to the pancreaticogastrostomy anastomosis, but there were no nodules in the remnant pancreas, and there was no indication of metastasis to the lymph nodes, liver, or lung (Fig. 3). Laboratory tests showed that there were no liver or kidney dysfunction, and the remaining hematologic parameters were almost within normal ranges. As IPMC recurrence was suspected, and the patient was scheduled for total pancreatectomy, subtotal gastrectomy and splenectomy. The total operating time was 328 min, and the intraoperative blood loss was 600 mL. The specimen was 3.5 cm(l)×3.8 cm(w), and IPMC invaded the serosa from the muscularis propria (Fig. 4a, b.). IPMC was observed in the remnant pancreas, extended into the stomach and was confirmed by histological findings [Pbt, pTS3, cystic type, IPMC invasive, pT3(stomach), int, INFa, ly0, v1,ne0, mpdx, pCHX, pDUX, pS0, pRP0, pV0, pA0, pOO1(stomach), pBCMX, pDPM0, pN0(0/13), R0]. However, there was no evidence that it spread to the lymph nodes, and pathological examination of frozen sections didn't identify adenocarcinoma at the resection margins (Fig. 5a–c). Morphological and immunohistochemical analyses showed that the cells were positive for genes CDX2, MUC2, and MUC5AC, and negative for MUC1 and MUC 6. Immunohistochemical analyses showed that the cells were Ki 67 positive with no p53 overexpression (Fig. 5d–j). Based on the pathological finding, this specimen was diagnosed with IPMC invasive recurrence with an intestinal epithelial subtype because of the similarity to the original pathological findings. The patient's postoperative course was uneventful, and he was discharged after 12 days. As a blood sugar control after total pancreatectomy, we introduced rapid-acting insulin analogue (Humalog® injection) 2 units after each meal and ultra-long acting insulin analogue (LANTUS Solo Star® 2 units after noon. A glucose value after total pancreatectomy is approximately 100–150 mg/dl, whereas we exchanged rapid-acting insulin analogue (Humalog® injection) 1 units after each meal and ultra-long acting insulin analogue (LANTUS Solo Star® 1 units after noon at 5 months after total pancreatectomy because the patient was sometimes suffered hypoglycemia. The patient chose follow-up examinations without adjuvant chemotherapy and is alive with no signs of cancer recurrence eight-months after surgery.

3. Discussion

IPMNs are classified further into four epithelial subtypes based on mucin expression and morphology: gastric, intestinal, pancreatobiliary and oncocytic [6]. The gastric subtype usually exhibits low- to intermediate-grade dysplasia but may rarely progress to an aggressive tubular-type adenocarcinoma. Although progression from gastric-subtype IPMN to cancer is relatively rare, one study found that 74% of IPMN -associated cancers were of the gastric subtype and had significantly worse survival rates compared to other IPMN derived cancers [7]. The other subtypes are associated with higher grades of dysplasia and malignant transformation. The intestinal subtype is the most common form of main duct IPMN and correlates with progression to colloid carcinoma. The pancre-

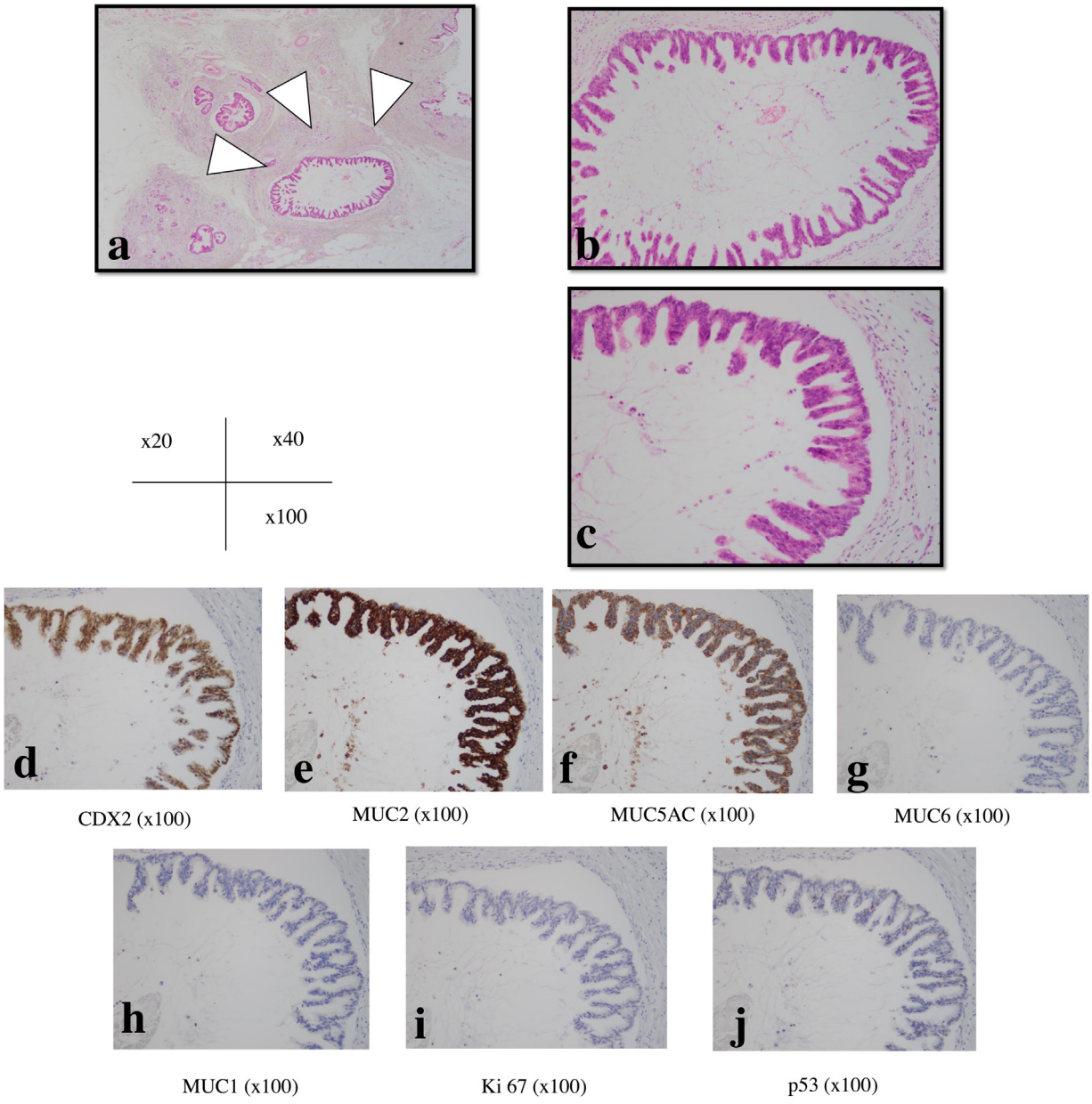

Fig. 5. Microscopic, morphological, and immunohistochemical findings.
(a) (b) (c) IPMC was observed in the remnant pancreas, and it extended into the stomach; however there was no evidence that it had spread to the lymph nodes, and no signs of adenocarcinoma at the resection margin were found by pathological examination of frozen sections.
(d)(e)(f)(g)(h)(i)(j) Immunohistochemical analyses showed that the cells were positive for CDX2, MUC2, and MUC5AC and negative for MUC1 and MUC6. Besides, immunohistochemical analyses showed that the cells were positive for Ki 67, and there was no overexpression for p53.

atobiliary subtype carries the highest prognostic because of its high progression rate to invasive tubular adenocarcinoma.

Recurrence risk factors are also attributed to IPMN histological subtypes, which recur at different rates (non-invasive IPMN: gastric 3.4%, intestinal 9.8%, pancreatobiliary 11.1%, oncocytic 0%) [8]. Preoperative identification of pancreatobiliary or intestinal subtypes would be benefical for risk stratification and resection planning.

Intrapancreatic recurrence of IPMN or pancreatic cancer could be explained by a close margin at the time of the original resection or by the finding HGD (PanIN-3) at the margins. The results are inconclusive regarding the influence of the margin on recurrence, partly because there is no consensus on the definition for margin positivity following IPMN resection [9]. White et al. defined a positive margin as any IPMN grade present at the margin, excluding PanIN-1 and -2, and reported recurrence in 17% of positive margins versus 2% of negative margins ($p = 0.02$) [10]. A meta-analysis comprising 12 studies with a total of 701 non-invasive IPMNs defined a positive margin as any dysplasia grade, excluding PanIN-1A and 1B, which yielded a 9.6% recurrence rate in positive margin resections compared to 3.7% in negative margin ($p = 0.01$) [11]. Most authors speculate that positive margins do not represent a local oncological resection failure since the resulting recurrence rarely occurs at the margin itself [11,12].

Recently, several cases of IPMC relapse following radical surgery for IPMN or IPMC were reported. The disease recurrence rate in the pancreatic remnants following the surgical removal of IPMC was 7–26% after a median follow-up period of 46 months and had an average excision ratio of 36% [3,13,14]. A Japanese multicenter study of 1074 IPMN patients also reported that the five-year and ten-year cumulative high-risk lesions incidences; malignant

IPMN progression and new PDAC development, in the remnant pancreas after IPMN surgical resection were 6.2% and 12.6%, respectively [15]. Several reports stated that the mean interval between resection and recurrence diagnosis was 18 ± 3 months; recurrence occurred 70% of cases within two years and 91% within three years of resection [3]. Others reported that the median postoperative disease-free interval was 38 months.

Alternatively, IPMNs may result from a pancreatic field defect comprised of diffusely unstable ductal epithelium prone to malignant degeneration [2,3,16]. From an oncologic perspective, multifocal disease and the likelihood of a widespread field defect argue in favor of the radical resection of all pancreatic tissue via total pancreatectomy. However, the magnitude of the postoperative morbidity related to the pancreatic state is generally considered too severe, except for those cases with the greatest recurrence risk. Therefore, current management guidelines recommend a limited segmental resection followed by ongoing, postoperative surveillance of the pancreatic remnant for most lesions meeting resection criteria [1].

After the initial surgery, the remnant pancreatic recurrence prognosis was reported to be between 16 and 27.2 months, the overall survival was two months, and the median survival time was between 10.7 and 13.5 months (equivalent to unresectable cases), between 16 and 26 months for PDAC, and between 7 and 24 months for IPMC after total pancreatectomy [17].

Our patient's recurrence may have been due to multifocal disease that developed a new cyst over time, rather than the resection margins. We considered the overall survival and median survival times and chose secondary surgery over chemotherapy despite the quality of life drawbacks that may make remnant or total pancreatectomy inappropriate for some patients (e.g. worsening of diabetes mellitus and exocrine dyfunction).

4. Conclusion

We completely cured a recurrent IPMC that arose in the remnant pancreas following pancreaticoduodenectomy for IPMC after follow-up period of 8months. Earlier detection through annual check-ups, periodical tumor markers, and imaging analyses is important. Moreover, remnant pancreatectomy is the preferred approach for treating remnant pancreatic carcinoma due to better median long-term survival outcome.

Declaration of Competing Interest

The authors report no declarations of interest.

Sources of funding

Not applicable.

Ethical approval

Approval of the study was granted by the Institutional Review Board of Department of Gastroenterological Center Surgery, Shunjukai Shiroyama Hospital, and written informed consent for publication was obtained from the patient.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content. Jun K, Toshikatsu N, and Takashi I analyzed histopathological features and drafted the manuscript. Jun K, Toshikatsu N, Masato O, and Kensuke F a team of attending doctors of the present case, earnestly discussed clinical problems. Atsushi T provided valuable advice and suggestions as a histopathologic consultant and contributed to part of the molecular study. All authors read and approved the final manuscript.

Registration of research studies

Not applicable.

Guarantor

Not applicable.

Provenance and peer review

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