



## Long-term Surgical Outcome of Noninvasive and Minimally Invasive Intraductal Papillary Mucinous Adenocarcinoma of the Pancreas

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**Abstract.** The objective of this study was to clarify the long-term outcome after surgical resection in patients with noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma. We performed a retrospective review of the clinicopathological features and outcome in patients who underwent pancreatic resection for noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma between November 1982 and December 1997 at Chiba University Hospital. Minimally invasive structures were pathologically observed in five cases. The mean age of patients with either noninvasive ( $n = 16$ ) or minimally invasive ( $n = 5$ ) adenocarcinoma was 61 years. Of the patients with minimally invasive adenocarcinoma, 4 had abdominal pain. Conversely, 7 patients with noninvasive adenocarcinoma had no complaint. The mean size of noninvasive and minimally invasive tumors was 2.5 cm (range 0.8 to 4.0) and 3.3 cm (range 2.5 to 4.5), respectively. The overall 5-year and 10-year survival rates for all 21 patients were 89% and 47%, respectively. Disease recurred in 3 patients; 2 patients with minimally invasive adenocarcinoma and 1 with noninvasive adenocarcinoma. Recurrence sites were peritoneum ( $n = 2$ ) and main pancreatic duct of the remnant pancreas ( $n = 1$ ); 5 disease-free patients died of unrelated causes. The remaining 13 patients are alive and disease free 3 to 12 years after surgery. Noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma had a favorable prognosis after surgical treatment.

Many cases of intraductal papillary mucinous tumor of the pancreas have been reported in recent years [1–12]. The prognosis for this neoplasm has proved to be more favorable than that for invasive ductal carcinoma. However, the long-term outcome after surgical resection in patients with noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma has not been fully clarified, because these neoplasms are uncommon compared to invasive ductal carcinoma. Furthermore, adenoma and adenocarcinoma were not divided for survival analysis in most studies of intraductal papillary mucinous tumors. Longer follow-up will be required to ensure cure, because these tumors have an indolent biological behavior. In this report, we analyze our 15-year experience with noninvasive and minimally invasive intraductal papillary mucinous adenocarcinomas.

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### Patients and Methods

Twenty-one patients with noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma underwent surgical resection at Chiba University Hospital between November 1982 and December 1997. Tumors showing massive invasion into the pancreatic parenchyma were excluded from the study. Patient follow up ranged from 33 months to 146 months (median 78 months). Intraductal papillary mucinous adenocarcinomas were classified into main duct type ( $n = 7$ ) and branch type ( $n = 14$ ), according to the dominant location of the tumor. Papillary adenocarcinomas originating in the main pancreatic duct or the duct of Santorini were defined as main duct type. Adenocarcinomas located in a branch of the pancreatic duct were defined as branch type. Most branch type tumors formed cystic lesions. These neoplasms were subdivided into noninvasive and minimally invasive tumors according to the Classification of Pancreatic Carcinoma [13] proposed by the Japan Pancreas Society. The clinicopathological features of noninvasive type and minimally invasive type, and also main duct type and branch type, were compared with regard to sex, age, symptoms, findings of imaging studies, size, tumor location, histopathological findings, and prognosis.

Statistical analysis was performed by chi-square and Student's *t*-test, when appropriate. Cumulative survival rates were generated by the Kaplan-Meier method. The overall survival curve includes all deaths. The survival curves were compared by the generalized Wilcoxon test. Differences were considered significant at  $p < 0.05$ .

### Results

The characteristics of the patients with noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma are shown in Table 1. Invasive structures were observed histopathologically in 5 cases (4 branch type, 1 main duct type). These tumors could be classified as noninvasive and as minimally invasive only by final histopathology. The classification could not be made surgically or preoperatively. The mean age of patients with either noninvasive ( $n = 16$ ) or minimally invasive ( $n = 5$ ) adeno-

**Table 1.** Comparison of characteristics between noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma.

	Noninvasive (n = 16)	Minimally invasive (n = 5)
Age (years)	61 (range 44–76)	61 (range 52–72)
Gender (male/female)	11/5	3/2
Size, mean (cm)	2.5 (range 0.8–4.0)	3.3 (range 2.5–4.5)
Type		
Main duct type	6	1
Branch type	10	4
Location		
Head	10	5
Head and body	1	0
Body	4	0
Tail	1	0
Diameter of MPD, mean (mm)	12	10

MPD: the main pancreatic duct.

**Table 2.** Operative procedures performed in the 21 patients with noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma.

	Noninvasive (n = 16)	Minimally invasive (n = 5)	Total (n = 21)
Whipple's PD	3	2	5
DpPHR	4	1	5
DP	5	0	5
Pylorus-preserving PD	3	1	4
Inferior head resection	1	1	2

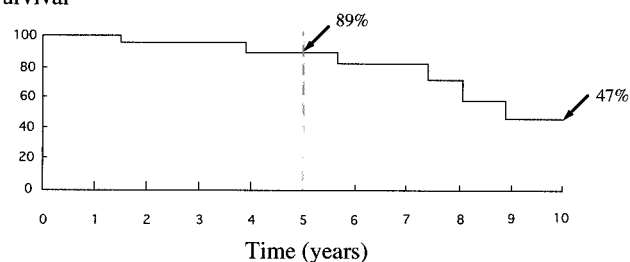
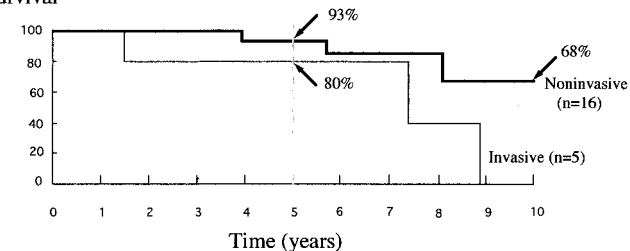
PD: pancreatoduodenectomy; DpPHR: duodenum-preserving pancreatic head resection; DP: distal pancreatectomy.

carcinoma was 61 years. Of the patients with minimally invasive adenocarcinoma, 4 had abdominal pain. Conversely, 7 patients with noninvasive adenocarcinoma had no complaint.

The mean size of noninvasive and minimally invasive tumors was 2.5 cm (range 0.8 to 4.0) and 3.3 cm (range 2.5 to 4.5). There was no significant difference between invasive and noninvasive tumors ( $p = 0.14$ ). In branch type adenocarcinomas, 86% of tumors were located in the pancreatic head, whereas only 43% of main duct type tumors were located in the pancreatic head.

Patients with noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma were treated by Whipple's pancreatoduodenectomy ( $n = 5$ ), duodenum-preserving pancreatic head resection ( $n = 5$ ), distal pancreatectomy ( $n = 5$ ), pylorus-preserving pancreatoduodenectomy ( $n = 4$ ), and inferior head resection of the pancreas ( $n = 2$ ) (Table 2). None of the 21 patients died within 30 days of operation, and all patients were discharged from hospital after surgery. Surgical reintervention was necessary in 1 patient because of intra-abdominal bleeding after duodenum-preserving pancreatic head resection. No tumors showed invasion of the surgical margin. No lymph node involvement or liver metastasis was observed at the time of operation in our series.

All of the patients were followed for more than 2 years after operation. The survival curves after surgical treatment are shown in Fig. 1. The overall 5-year and 10-year survival rates for all 21 patients were 89% and 47%, respectively. Five-year survival rates for the patients with noninvasive adenocarcinoma ( $n = 16$ ) and minimally invasive adenocarcinoma ( $n = 5$ ) were 93% and 80%, respectively (Fig. 2). There was no significant difference between

**%Survival****1****%Survival****2****Fig. 1.** Survival rates for the patients with noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma ( $n = 21$ ).**Fig. 2.** Survival rates for the patients with noninvasive adenocarcinoma ( $n = 16$ ) and minimally invasive adenocarcinoma ( $n = 5$ ). No significant difference was found between the groups; generalized Wilcoxon test;  $p = 0.13$ .**Table 3.** Numbers of disease recurrence and death after surgical treatment.

	Noninvasive (n = 16)	Minimally invasive (n = 5)	Total (n = 21)
Number of deaths	5	3	8
Death due to recurrence	0	2	2
Death from other cause in patients with recurrence	1	0	1
Death from other cause in disease-free patients	4	1	5

the two groups ( $p = 0.13$ ). Five-year survival rates for the patients with main duct type adenocarcinoma ( $n = 7$ ) and branch type adenocarcinoma ( $n = 14$ ) were 100% and 84%, respectively. There was no significant difference in survival between the groups ( $p = 0.28$ ). Numbers of disease recurrence and deaths after surgery are shown in Table 3. Recurrent disease occurred in 3 patients: 2 patients with minimally invasive adenocarcinoma and a patient with noninvasive adenocarcinoma. Recurrence sites were peritoneum ( $n = 2$ ) and main pancreatic duct of the remnant pancreas ( $n = 1$ ). Two patients with minimally invasive tumor died of peritoneal dissemination 1.5 years and 8 years after the primary operation, respectively. One patient with noninvasive tumor died of respiratory failure from lung fibrosis and fungal infection 10 years after the operation, though recurrence was present in the remnant pancreas. Five disease-free patients died of unrelated causes, such as other cancers, brain infarctions, and a heart failure. Two disease-free patients died of other cancers. One patient developed both hepatocellular carcinoma and carcinoma of the ampulla of Vater, and another patient developed bile duct carcinoma. There are no patients alive with disease recurrence. The remaining 13 patients are alive and disease free 3 to 12 years after surgery.

## Discussion

Intraductal papillary mucinous tumor is a recently established clinical entity that includes a spectrum of lesions ranging from benign to malignant infiltrating tumors. Growing numbers of intraductal papillary mucinous tumors have been reported since the 1980s. However, the prognosis for intraductal papillary mucinous adenocarcinoma has not been fully understood, because adenoma and adenocarcinoma were not divided for survival analysis in most studies. In this study, the overall 5-year and 10-year survival rates for patients with noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma were 89% and 47%, respectively. Only 3 patients developed recurrent disease after surgical resection. Our data suggest that patients with noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma had a favorable prognosis after surgical treatment. There was no significant difference between noninvasive tumors and minimally invasive tumors ( $p = 0.13$ ). Sugiyama and associates also reported an 81% 5-year survival rate for intraductal papillary adenocarcinoma [14]. Thus, surgical resection could play an important role in treating noninvasive and minimally invasive intraductal papillary mucinous adenocarcinoma.

However, Cuillerier et al. reported that patients with invasive intraductal papillary carcinoma frequently developed recurrent disease [15]. Is the existence of invasive structures beyond the pancreatic duct wall associated with the prognosis? Recurrence occurred in 2 of 5 patients with minimally invasive adenocarcinoma and in 1 of 16 patients with noninvasive tumors in our series. The statistical analysis did not show a significant difference in survival between noninvasive and minimally invasive tumors. The patients with minimally invasive tumor had a good 5-year survival (80%). These results suggest that patients with minimally invasive tumor have a more favorable prognosis than patients with invasive intraductal papillary adenocarcinoma including a massive invasive component.

Terris and colleagues reported that the main pancreatic duct type showed invasive carcinoma in 11 (37%) and in situ carcinoma in 6 (20%) of 30 patients, respectively, and the branch type showed significantly less aggressive lesions with no invasive carcinoma histologically [16]. We have recently reported that 88% of main duct type tumors were adenocarcinomas and only 46% of branch type tumors were adenocarcinomas [17]. Kobari reported that the 5-year survival rate for main duct tumors ( $n = 13$ ) was 47%, and 4 patients with main duct tumors had local recurrence [10]. However, our results showed that all patients with main duct type adenocarcinoma ( $n = 7$ ) survived for 5 years after surgical treatment. There was no significant difference in survival between main duct type and branch type ( $p = 0.28$ ).

Standard pancreatic resection or total pancreatectomy has been performed for intraductal papillary mucinous tumors [7–9, 18]. Limited pancreatic resection remains controversial [19–21]. Cuillerier and associates reported one case of recurrence after total pancreatectomy, 6 after partial pancreatectomy with a disease-free margin, and 6 after partial pancreatectomy with involvement of the margin [15]. Sho and colleagues reported that the major site of recurrence was remnant pancreas [22]. In our series, the sites of recurrence during follow-up were peritoneum or the main pancreatic duct of the remnant pancreas. Two patients with minimally invasive tumor died of peritoneal dissemination 1.5 and 8 years after the primary operation, respectively. One patient with non-

invasive tumor died of respiratory failure from lung fibrosis and fungal infection 10 years after the operation, though recurrence was present in the remnant pancreas. We performed inferior head resection for 2 patients with branch type intraductal papillary mucinous adenocarcinoma [20]. One patient with noninvasive intraductal papillary mucinous adenocarcinoma survived 5 years after inferior head resection, whereas the other patient with minimally invasive intraductal papillary mucinous adenocarcinoma died of peritoneal dissemination 18 months after inferior head resection. We think that complete extirpation of the tumor with a free margin is essential for treating adenoma, noninvasive adenocarcinoma, and minimally invasive adenocarcinoma. The favorable prognosis and low-grade malignant behavior of noninvasive and minimally invasive tumors suggest that a small involvement may enable the surgeon to do partial duodenum-preserving resections.

Preoperative differential diagnosis between adenoma, noninvasive adenocarcinoma, and minimally invasive adenocarcinoma is difficult and challenging. The preoperative diagnosis of this neoplasm may be aided by imaging studies and endoscopic examinations [23, 24]. Irie et al. reported that diffuse main pancreatic duct dilatation greater than 15 mm (main duct type) or any main pancreatic duct dilatation (branch duct type) detected by magnetic resonance imaging is strongly associated with malignancy [25]. However, precise differential diagnosis between invasive and noninvasive intraductal papillary mucinous adenocarcinoma may be impossible because of minimal invasion beyond the pancreatic duct wall. In patients with branch type, all invasive tumors showed diffuse main pancreatic duct dilatation greater than 8 mm. Preoperative imaging studies showed that the cystic tumor was greater than 3 cm in all cases of invasive adenocarcinoma. Thus, care must be taken to ensure a negative margin when the tumor is larger than 3 cm with diffuse main pancreatic duct dilatation.

**Résumé.** Le but de cette étude a été de clarifier l'évolution à long terme après résection chirurgicale des patients porteurs d'adénocarcinome papillaire mucineux du pancréas, noninvasif et minimalement invasif, grâce à une revue rétrospective des données cliniques et pathologiques des patients traités entre novembre 1982 et décembre 1997 à l'Hôpital Universitaire de Chiba. Un envahissement minime a été observé en anatomopathologie dans cinq cas. L'âge moyen des patients porteurs d'adénocarcinome non-invasif ( $n = 16$ ) ou minimal invasif ( $n = 5$ ) a été, de 61 ans. Parmi les patients présentant un adénocarcinome minimal invasif, quatre avaient des douleurs abdominales. En revanche, sept patients porteurs d'adénocarcinome noninvasif n'avaient aucune plainte. La taille moyenne des tumeurs noninvasives et minimalement invasives a été, respectivement, de 2.5 cm (extrêmes: 0.8–4.0) et de 3.3 cm (extrêmes: 2.5–4.5). La survie globale à 5 et à 10 ans pour les 21 patients a été, respectivement, de 89% et de 47%. On a observé une récurrence chez trois patients; deux patients ayant un adénocarcinome minimalement invasif, et un patient porteur d'un adénocarcinome noninvasif. Les sites de récurrences ont été péritonéal ( $n = 2$ ) et le canal de Wirsung du pancréas restant ( $n = 1$ ). Cinq patients sont décédés de causes sans rapport avec leur cancer (sans maladie). Les 13 autres patients sont en vie sans récurrence 3–12 ans après chirurgie. Le pronostic de l'adénocarcinome papillaire mucineux noninvasif et minimalement invasif est favorable après traitement chirurgical.

**Resumen.** El objetivo del estudio fue esclarecer el resultado a largo plazo de la resección quirúrgica en pacientes con adenocarcinoma papilar mucinoso intraductal no invasor o mínimamente invasor del páncreas. Se efectuó una revisión retrospectiva de las características clínico patológicas y del resultado en pacientes con este tipo de lesión sometidos a resección pancreática entre noviembre de 1982 y diciembre de 1997 en el Hospital Universitario de Chiba. En cinco casos se observaron

estructuras mínimamente invasoras. La edad promedio de los pacientes con adenocarcinoma no invasor ( $n = 16$ ) y mínimamente invasor ( $n = 5$ ) fue 61 y 61 años, respectivamente. De los pacientes con adenocarcinoma mínimamente invasor, cuatro presentaban dolor abdominal. En contraste, siete con adenocarcinoma no acusaron síntomas. El tamaño promedio fue 2.5 cm (rango: 0.8–4.0) para el adenocarcinoma no invasor y 3.3 cm (rango: 2.5–4.5) para el mínimamente invasor. Las tasas globales de supervivencia a 5 y 10 años para los 21 pacientes fueron 89% y 47% respectivamente. Se presentó enfermedad recurrente en 3 pacientes, dos con mínimamente invasor y uno con no invasor. Los sitios de recurrencia fueron el peritoneo ( $n = 2$ ) y el canal pancreático del páncreas remanente ( $n = 1$ ). Cinco pacientes libres de enfermedad murieron por otras causas. Los restantes 13 pacientes se encuentran vivos y libres de enfermedad a los 3–12 años después de la cirugía. El adenocarcinoma papilar mucinoso no invasor y mínimamente invasor exhibió un pronóstico favorable luego de la cirugía.

## References

- Ohhashi K, Murakami Y, Maruyama M, et al. Four cases of "mucin-producing" cancer of the pancreas on specific findings of the papilla of Vater (in Japanese; abstract in English). *Prog. Dig. Endosc.* 1982;20:348–351
- Itai Y, Kokubo T, Atomi Y, et al. Mucin-hypersecreting carcinoma of the pancreas. *Radiology* 1987;165:51–55
- Rickaert F, Cremer M, Deviere J, et al. Intraductal mucin-hypersecreting neoplasms of the pancreas. A clinicopathologic study of eight patients. *Gastroenterology* 1991;101:512–519
- Nishihara K, Fukuda T, Tsuneyoshi M, et al. Intraductal papillary neoplasm of the pancreas. *Cancer* 1993;72:689–696
- Santini D, Campione O, Salerno A, et al. Intraductal papillary-mucinous neoplasm of the pancreas. A clinicopathologic entity. *Arch. Pathol. Lab. Med.* 1995;119:209–213
- Loftus EV Jr, Olivares-Pakzad BA, Batts KP, et al. Intraductal papillary-mucinous tumors of the pancreas: clinicopathologic features, outcome, and nomenclature. Members of the Pancreas Clinic, and Pancreatic Surgeons of Mayo Clinic. *Gastroenterology* 1996;110:1909–1918
- Tenner S, Carr-Locke DL, Banks PA, et al. Intraductal mucin-hypersecreting neoplasm "mucinous ductal ectasia": endoscopic recognition and management. *Am. J. Gastroenterol.* 1996;91:2548–2554
- Shyr YM, Su CH, Tsay SH, et al. Mucin-producing neoplasms of the pancreas. Intraductal papillary and mucinous cystic neoplasms. *Ann. Surg.* 1996;223:141–146
- Madura JA, Wiebke EA, Howard TJ, et al. Mucin-hypersecreting intraductal neoplasms of the pancreas: a precursor to cystic pancreatic malignancies. *Surgery* 1997;122:786–792
- Kobari M, Egawa S, Shibuya K, et al. Intraductal papillary mucinous tumors of the pancreas comprise 2 clinical subtypes: differences in clinical characteristics and surgical management. *Arch. Surg.* 1999;134:1131–1136
- Bassi C, Procacci C, Zamboni G, et al. Intraductal papillary mucinous tumors of the pancreas. Verona University Pancreatic Team. *Int. J. Pancreatol.* 2000;27:181–193
- Adsay NV, Longnecker DS, Klimstra DS. Pancreatic tumors with cystic dilatation of the ducts: intraductal papillary mucinous neoplasms and intraductal oncocytic papillary neoplasms. *Semin. Diagn. Pathol.* 2000;17:16–30
- Japan Pancreatic Society Classification of Pancreatic Carcinoma, 1st English Edition. Tokyo, Kanehara & Co. Ltd., 1996:32–33
- Sugiyama M, Atomi Y, Kuroda A. Two types of mucin-producing cystic tumors of the pancreas: diagnosis and treatment. *Surgery* 1997;122:617–625
- Cuillerier E, Cellier C, Palazzo L, et al. Outcome after surgical resection of intraductal papillary and mucinous tumors of the pancreas. *Am. J. Gastroenterol.* 2000;95:441–445
- Terris B, Ponsot P, Paye F, et al. Intraductal papillary mucinous tumors of the pancreas confined to secondary ducts show less aggressive pathologic features as compared with those involving the main pancreatic duct. *Am. J. Surg. Pathol.* 2000;24:1372–1377
- Nakagohri T, Kenmochi T, Kainuma O, et al. Intraductal papillary mucinous tumors of the pancreas. *Am. J. Surg.* 1999;178:344–347
- Horvath KD, Chabot JA. An aggressive resectional approach to cystic neoplasms of the pancreas. *Am. J. Surg.* 1999;178:269–274
- Sperti C, Pasquali C, Ferronato A, et al. Median pancreatectomy for tumors of the neck and body of the pancreas. *J. Am. Coll. Surg.* 2000;190:711–716
- Nakagohri T, Kenmochi T, Kainuma O, et al. Inferior head resection of the pancreas for intraductal papillary mucinous tumors. *Am. J. Surg.* 2000;179:482–484
- Siech M, Mattfeldt T, Schlosser W, et al. Duodenum-preserving pancreatic head resection in patients with benign and borderline tumors of the pancreatic head. *Langenbecks Arch. Surg.* 2000;385:229–233
- Sho M, Nakajima Y, Kanehiro H, et al. Pattern of recurrence after resection for intraductal papillary mucinous tumors of the pancreas. *World J. Surg.* 1998;22:874–878
- Cellier C, Cuillerier E, Palazzo L, et al. Intraductal papillary and mucinous tumors of the pancreas: accuracy of preoperative computed tomography, endoscopic retrograde pancreatography and endoscopic ultrasonography, and long-term outcome in a large surgical series. *Gastrointest. Endosc.* 1998;47:42–49
- Yamaguchi T, Hara T, Tsuyuguchi T, et al. Peroral pancreatoscopy in the diagnosis of mucin-producing tumors of the pancreas. *Gastrointest. Endosc.* 2000;52:67–73
- Irie H, Honda H, Aibe H, et al. MR cholangiopancreatographic differentiation of benign and malignant intraductal mucin-producing tumors of the pancreas. *AJR Am. J. Roentgenol.* 2000;174:1403–1408