Table 6 Recent reports of the incidence of benign hilar strictures in surgically resected cases

	Total number of resected specimen	Number of benign biliary stricture	Autoimmune-like sclerosing cholangitis	IgG4-related sclerosing cholangitis	Incidence of IgG4-related SC in ASC (%)
Corvera et al. [3]	275	22 (8.0%)[a]	13 (59.1%)[b]	2 (9.1%)[b]	15.4
Erdogan et al. [4]	185	32 (17.3%)[a]	15 (46.9%)[b]	2 (6.2%)[b]	13.3
Present study	176	21 (11.9%)[a]	5 (23.8%)[b]	1 (4.8%)[b]	20.0

ASC Autoimmune-like sclerosing cholangitis

[a] Percentage among total number of resected case

[b] Percentage among number of benign biliary stricture

A summary of cases in the literature of benign proximal stricture of the bile duct presumably diagnosed as cholangiocarcinoma is shown in Table 5 [1–8, 25]. Of these, PSC is an important differential diagnosis in patients with suspected proximal biliary stricture. The prevalence of PSC is estimated to be between three and eight cases per 100,000 people [26, 27]; however, the prevalence of patients with PSC varies worldwide [22, 26, 28, 29]. Moreover, due to the consistently low (0–1.1%) incidence of PSC in malignant hilar masquerade, only a few studies have clearly described the incidence of PSC as that of malignant masquerade.

Recent reports of the incidence of benign hilar strictures in surgically resected cases, particularly autoimmune-like sclerosing cholangitis and IgG4-positive chronic cholangitis preoperatively diagnosed as hilar carcinoma, are summarized in Table 6 [3, 4]. Including our results, the incidence of benign biliary strictures ranged from 8.0 to 17.3%. Among the cases diagnosed as benign biliary obstructions, the incidence of autoimmune-like disease and possible IgG4-related sclerosing cholangitis ranged from 23.8 to 59.1 and 4.8 to 9.1%, respectively. These data indicate that IgG4-related sclerosing cholangitis accounts for 13.3–20% of autoimmune-like sclerosing cholangitis, implying that potentially there are several uncategorized types of autoimmune-like sclerosing cholangitis. Indeed, histopathological or immunohistochemical findings similar to our cases (case 3 and 5) with marked lymphoplasmacytic infiltration and lymph follicle formation with germinal centers have been found in previous large studies [3]. Their presented cases could belong to the same category as our case 3 and 5.

One important reason for classifying benign sclerosing cholangitis of unknown origin is to determine an appropriate treatment strategy and estimation of the prognosis. Sclerosing cholangitis can be divided into two subtypes: (1) IgG4-related sclerosing cholangitis, which responds well to corticosteroid therapy and has a good prognosis, and (2) PSC, which responds well to corticosteroids and requires liver transplantation [11, 13, 30]. The clinical courses and outcomes of our five cases varied; case 3 developed recurrent cholangitis 2 months after the surgery,

which resulted in a progressive worsening of liver function despite immunosuppressive therapy, whereas case 1 had no sign of recurrent disease after a long-term follow-up. Few studies have reported the response to immunosuppressive therapy or the long-term prognosis of patients with benign sclerosing cholangitis of hilar malignant masquerade. However, in order to classify benign sclerosing cholangitis of unknown origin, it is important to examine not only the characteristics of the disease, but also the treatment strategy and long-term prognosis.

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Inferior head resection of the pancreas for intraductal papillary mucinous neoplasms

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Abstract

Background Previous reports have suggested that patients with intraductal papillary mucinous neoplasm (IPMN) have a favorable prognosis after surgical resection. Thus, a variety of types of partial pancreatic resections have been advocated for treating these low-grade malignant tumors. However, the surgical outcome of such limited pancreatectomy has not been fully clarified.

Methods We performed a retrospective review of the clinicopathologic features and surgical outcome in 15 patients who underwent inferior head resection for IPMN at the Chiba University Hospital and National Cancer Center Hospital East between July 1994 and January 2007.

Results There were 13 patients with noninvasive IPMNs (10 adenomas and 3 noninvasive carcinomas) and 2 patients with minimally invasive intraductal papillary mucinous carcinoma (minimally invasive IPMNs). Complete tumor removal (R0 resection) was performed in four patients (80%) with intraductal papillary mucinous carcinoma. Subsequent pancreatoduodenectomy was performed in one patient because of noninvasive carcinoma with multiple mucous lakes in the pancreatic parenchyma. Values for *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid excretion test results before ($n = 13$) and after ($n = 13$) the operation were 70.7 and 66.1, showing no significant difference. The 2-h glucose levels in the 75 g oral glucose tolerance test before ($n = 13$) and after ($n = 13$) the operation were 133 and 146 mg/dl, respectively, showing no significant difference. Pancreatic fistula occurred in 7 (47%) patients. Overall morbidity and mortality rates were 67 and 0%, respectively. The overall 1-, 3-, 5-, and 10-year survival rates for the 15 patients were 100, 79, 79, and 71%, respectively. The 1-, 3-, 5-, and 10-year survival rates for patients with noninvasive IPMN ($n = 13$) and those with minimally invasive IPMN ($n = 2$) were 100, 92, 92, and 83%; and 100, 0, 0, and 0%, respectively. There was a significant difference in survival between patients with noninvasive IPMN and those with minimally invasive IPMN ($p = 0.0005$). No patient with noninvasive IPMN developed recurrent disease. One patient with minimally invasive IPMN died of recurrent peritoneal dissemination 18 months after margin-positive R1 resection. Two patients died of pancreatic ductal adenocarcinoma, 30 and 78 months after inferior head resection.

Conclusions Pancreatic endocrine and exocrine function was well preserved after inferior head resection. Pancreatic fistula occurred more frequently after inferior head resection than with conventional pancreatoduodenectomy. Patients with noninvasive IPMN had favorable survivals after this procedure. However, one patient with minimally invasive IPMN with margin-positive R1 resection died of recurrent disease. Thus, margin-negative R0 resection should be performed for IPMN.

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Student's t test. Cumulative survival rates were generated by the Kaplan–Meier method. The survival curves were compared by the log-rank test. Differences were considered significant at $p < 0.05$.

Introduction

An increasing number of cases of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas have been reported in recent years [1–13]. Histopathologic studies have revealed that IPMN shows a spectrum of epithelial dysplasia ranging from adenoma to invasive carcinoma. The presence of an invasive component is strongly associated with poor survival [14–17]. In contrast, patients with a noninvasive neoplasm, such as adenoma or noninvasive carcinoma, have a favorable prognosis after surgical resection [17–19]. Thus, a variety of types of partial pancreatic resections have been advocated for treating these low-grade malignant tumors [20–24]. However, the appropriate indications and the surgical outcome of such limited partial pancreatectomies have not been fully clarified because of the limited number of cases. Accordingly, we performed a retrospective review of the clinicopathologic features and outcome in 15 patients who underwent inferior head resection for IPMN.

Patients and methods

Fifteen consecutive patients with IPMN who underwent inferior head resection at the Chiba University Hospital and National Cancer Center Hospital East between July 1994 and January 2007 were retrospectively analyzed. Both the uncinate process and the pancreatic parenchyma around the duct of Wirsung were resected in the inferior head resections. After excision of the inferior head of the pancreas, pancreaticojejunostomy or pancreaticoduodenostomy was performed. The details of this procedure have been described in a previous report [22]. Patient follow up ranged from 24 to 164 months (median 81 months). Overall survival analysis included all deaths, including deaths due to an unrelated cause. IPMN was classified as noninvasive IPMN ($n = 13$) or minimally invasive intraductal papillary mucinous carcinoma (minimally invasive IPMN) ($n = 2$). Noninvasive IPMN was subdivided into adenoma ($n = 10$) and noninvasive carcinoma ($n = 3$) according to the *Classification of pancreatic carcinoma* proposed by the Japan Pancreas Society [25]. Histopathologic findings were evaluated according to this classification.

Exocrine and endocrine pancreatic function was evaluated by the N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) excretion test and the 75-g oral glucose tolerance test (OGTT). Statistical analysis was performed by

Results

The characteristics of the patients with IPMN who underwent inferior head resection are shown in Table 1. There were 13 men and 2 women, and the mean age of patients with IPMN was 64 years. Six patients (40%) had abdominal pain and 9 (60%) had no symptoms. The mean size of the tumor was 3.2 cm (range 1.0–6.4 cm), and the mean diameter of the main pancreatic duct was 5.8 mm (range 2.0–13 mm). There was no significant difference in tumor size or in the diameter of the main pancreatic duct between patients with noninvasive IPMN and those with minimally invasive IPMN. All tumors were classified as branch-duct type. The surgical margin was positive for adenoma in three patients with noninvasive IPMN and one patient with minimally invasive IPMN. The surgical margin was positive for carcinoma in one patient with minimally invasive IPMN. Intraoperative frozen section was not performed in this patient. Complete tumor removal (R0 resection) was performed in four patients (80%) with intraductal papillary mucinous carcinoma. No patient had lymph node metastasis. Subsequent pancreatoduodenectomy was performed in one patient because of noninvasive carcinoma with multiple mucous lakes in the pancreatic parenchyma. BT-PABA excretion test results before ($n = 13$) and after ($n = 13$) the operation were 70.7 and 66.1, showing no significant difference. The 2-h glucose levels of the 75-g OGTT before ($n = 13$) and after ($n = 13$) the operation were 133 and 146 mg/dl, respectively, showing no significant difference.

Pancreatic fistula occurred in 7 of the 15 patients (47%). Two patients underwent reoperation for intraabdominal hemorrhage due to pancreatic fistula. Delayed gastric emptying and bile leakage occurred in one patient. There were no in-hospital deaths. Overall morbidity and mortality rates were 67 and 0%, respectively.

The survival curves following inferior head resection are shown in Fig. 1. The overall 1-, 3-, 5-, and 10-year survival rates for the 15 patients were 100, 79, 79, and 71%, respectively. The 1-, 3-, 5-, and 10-year survival rates for patients with noninvasive IPMN ($n = 13$) and those with minimally invasive IPMN ($n = 2$) were 100, 92, 92, and 83%; and 100, 0, 0, and 0%, respectively. There was a significant difference in survival between the patients with noninvasive IPMN and those with minimally invasive IPMN. Regardless of the margin status for adenoma, no patient with noninvasive IPMN developed recurrent

Table 1 Characteristics of patients with intraductal papillary mucinous neoplasm who underwent inferior head resection

	Total (n = 15)	Noninvasive (n = 13)	Minimally invasive (n = 2)
Age, years (mean)	64	64	64
Gender (male/female)	13/2	11/2	2/0
Symptoms (%)			
Abdominal pain	6 (40%)	5 (38%)	1 (50%)
Back pain	1 (7%)	0	1 (50%)
General malaise	1 (7%)	1 (8%)	0
No symptoms	9 (60%)	8 (62%)	1 (50%)
Size, cm (mean)	3.2 (range 1.0–6.4)	3.1 (range 1.0–6.4)	3.7 (range 2.5–4.8)
Diameter of MPD, mm (mean)	5.8 (range 2.0–13)	5.4 (range 2.0–8.0)	8.0 (range 3.0–13)
Tumor type			
Branch-duct type	15	13	2
Histological findings			
Adenoma	10	10	0
Adenocarcinoma	5	3	2
Margin status			
Positive for adenoma	4	3	1
Positive for carcinoma	1	0	1
Subsequent PD	1	1	0
Number of recurrences	1	0	1

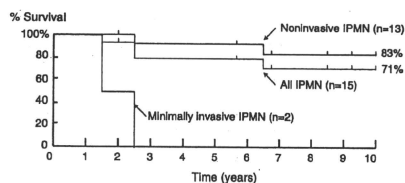*PD* pancreatoduodenectomy, *MPD* main pancreatic duct

Fig. 1 Survival rates for patients with noninvasive intraductal papillary mucinous neoplasm (*IPMN*; n = 13) and those with minimally invasive IPMN (n = 2)

disease. In contrast, one patient with minimally invasive IPMN died of recurrent peritoneal dissemination 18 months after margin-positive R1 resection. Two disease-free patients with adenoma died of unrelated causes; invasive ductal adenocarcinoma of the body of the pancreas 78 months after the inferior head resection, and respiratory failure 30 months after the operation. One disease-free patient with noninvasive carcinoma died of cerebral infarction 164 months after the operation. One disease-free patient with minimally invasive carcinoma died of invasive ductal adenocarcinoma of the head of the pancreas 30 months after the inferior head resection. Histological examination revealed a distinct difference in findings between minimally invasive IPMN and invasive ductal adenocarcinoma (Fig. 2a, b).

Discussion

We have herein reported the surgical outcome of IPMN after inferior head resection of the pancreas. This procedure removes the uncinate process and the pancreatic parenchyma around the duct of Wirsung [22]. The duodenum, bile duct, and superior part of the pancreatic head around the duct of Santorini are preserved. Thus, this is a type of duodenum-preserving partial pancreatic head resection. Because the field of resection is reduced in this procedure, pancreatic endocrine and exocrine function is well preserved after the operation.

Previous reports have suggested that patients with noninvasive IPMN have a favorable prognosis after surgical resection [16–19]. Thus, a variety of types of partial pancreatic resections have been advocated for treating these low-grade malignant tumors [20–24]. Takada [20] presented the procedure of ventral pancreatectomy. He resected only the ventral segment of the pancreas, without an anastomosis between the main pancreatic duct and the gastrointestinal tract. The field of resection in inferior head resection is similar to that in ventral pancreatectomy. Takada [20] and Ryu et al. [21] reported that the ventral and dorsal segment could be surgically separated, because the pancreas is formed by the fusion of the ventral and dorsal pancreatic anlagens. However, it might be difficult to accurately determine the demarcation between the ventral segment and the dorsal segment.

Fig. 2 Histological examination revealed a distinct difference in findings between minimally invasive IPMN and invasive ductal adenocarcinoma. **a** Microscopic findings of IPMN. Histological examination revealed marked papilla formation with significant architectural and nuclear atypia (hematoxylin and eosin, magnification ×100). **b** Microscopic findings of peritoneal dissemination from invasive ductal adenocarcinoma of the head of the pancreas. Histological examination showed moderately differentiated tubular adenocarcinoma with an intense desmoplastic reaction (hematoxylin and eosin, magnification ×100)

In the present study, overall morbidity and mortality after inferior head resection were 67 and 0%, respectively. Pancreatic fistula occurred more frequently with the inferior head resection than with conventional pancreatoduodenectomy. The wider cut surface of the pancreas after inferior head resection may lead to more frequent pancreatic fistula formation. Small branches of the pancreatic duct should be ligated or transfixed with many fine sutures during division of the pancreatic head. Furthermore, subsequent pancreatoduodenectomy was performed in one patient with noninvasive IPMN, because histological examination revealed multiple mucous lakes in the pancreatic parenchyma.

Intraductal papillary mucinous neoplasm is frequently classified as noninvasive IPMN and invasive IPMN. An indolent character and favorable outcome for noninvasive IPMN have been described recently [16–19]. In contrast, poor survival results have been reported for invasive IPMN [14–16, 26]. In the present study, the 5-year survival rate for noninvasive IPMN was 92%. In this study, regardless of the margin status for adenoma, no patient with noninvasive IPMN developed recurrent disease. Patients with noninvasive IPMN showed favorable survival after inferior head resection. However, one patient with minimally invasive IPMN with margin-positive R1 resection died of recurrent disease. Previous reports have suggested that patients with minimally invasive IPMN had favorable survivals compared with survivals in those with noninvasive IPMN [17–19]. Thus, better survival results could be achieved by margin-negative R0 resection even in minimally invasive IPMN. Care must be taken to ensure complete extirpation with a free margin. Frozen sections of the surgical margin would be useful for evaluating the margin status of IPMN [27]. If the transection margins in frozen sections are involved with carcinoma, such limited resections should be avoided, and pancreatoduodenectomy should be performed for IPMN. Further studies are needed to evaluate the efficacy of limited partial pancreatic resection for IPMN.

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Case Report

Invasive Micropapillary Carcinoma of the Ampulla of Vater with Extensive Lymph Node Metastasis: Report of a Case

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Abstract
Invasive micropapillary carcinoma is characterized by extensive lymph node metastasis and a poor prognosis. This histological variant was first described in breast cancer, with a few subsequent reports of it in the ampullo-pancreato-biliary region. We report a case of invasive micropapillary carcinoma of the papilla of Vater. A 53-year-old man was admitted to our hospital with signs of obstructive jaundice. Detailed investigations revealed a tumor in the periampullary region, and pancreatoduodenectomy was performed for cancer of the ampulla of Vater. Microscopic examination of the resected specimen revealed a tumor composed mainly of carcinoma cells arranged in micropapillary structures, with extensive regional lymph node metastasis. The patient had an uneventful postoperative course and was followed up in the outpatient clinic. Tumor recurrence with progressive ascites and hydronephrosis was found 8 months after surgery, and the patient died of the disease 20 months after surgery.

Key words Invasive micropapillary carcinoma · Papilla of Vater cancer · Ampullo-pancreato-biliary region

Introduction

Invasive micropapillary carcinoma (IMPC) was initially described as a histological variant of breast cancer,[1] characterized by delicate filiform processes and infiltrating clusters of micropapillary aggregates without central vascular cores.[2,3] Invasive micropapillary carcinoma of the breast has a high propensity to invade the lymphatic system with extensive metastasis to the axillary lymph

nodes; thus, it is nearly always associated with a poor prognosis.[1,4] Invasive micropapillary carcinoma of the urinary bladder carcinoma, ovary, and colon has also been reported.[5-7] However, few reports have described IMPC of the ampullo-pancreato-biliary region, and its clinicopathological features remain largely unknown. We report a case of IMPC of the papilla of Vater, with extensive lymph metastasis, resulting in a dismal outcome.

Case Report

A 53-year-old man was referred to our department with symptoms of obstructive jaundice, suggestive of cancer of the ampulla of Vater. He had initially presented to another hospital, where elevated serum bilirubin and hepatobiliary enzyme levels were detected. His family history was noncontributory to his condition. Endoscopic retrograde cholangiopancreatography demonstrated dilatation with a focal stenotic area in the lowermost common bile duct (Fig. 1a). Dynamic computed tomography and magnetic resonance imaging showed an enhanced tumor in the papilla of Vater and no evidence of metastasis in the liver. Upper gastrointestinal endoscopy showed an elevated and eroded area in the papilla of Vater (Fig. 1b), and histological examination of the biopsy specimen from the lesion revealed adenocarcinoma. We diagnosed cancer of the ampulla of Vater, and the patient underwent pancreatoduodenectomy.

Macroscopically, the tumor was 30 × 16mm in size with an irregular surface, and it was seen as an enlarged papilla of Vater (Fig. 2a). Histopathological examination revealed that the tumor consisted of an invasive micropapillary component and a small area of typical adenocarcinoma (Fig. 2b). The tumor was characterized by small round to ovoid micropapillary tumor cell clusters with no fibrovascular cores, lying within clefts (Fig.
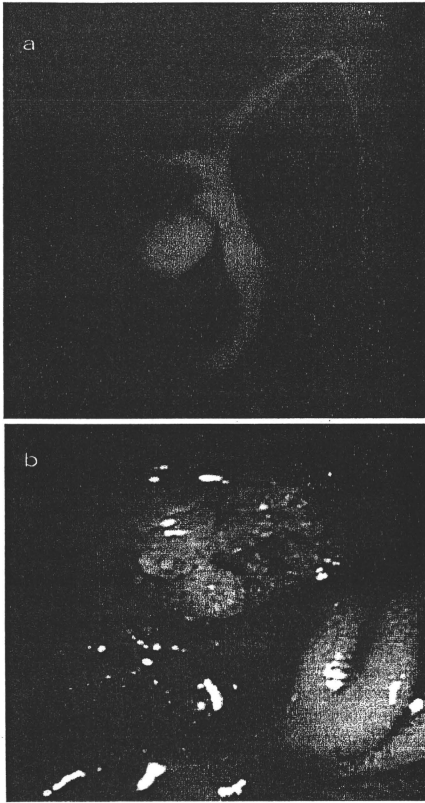
Fig. 1. a Endoscopic retrograde cholangiopancreatography showed dilatation with a focal stenotic area in the lowest point of the common bile duct, suggesting a tumor in the periampullary region. b Upper gastrointestinal endoscopy showed an elevated and eroded area in the papilla of Vater

2c). In most areas of the tumor, the micropapillary clusters were closely packed with scant intervening stroma. The cells had a moderate amount of eosinophilic cytoplasm and a moderate degree of nuclear atypia. There was marked lymphatic invasion, but no obvious venous invasion. Tumor metastasis was seen in all six lymph nodes along the hepatoduodenal ligament, in five of seven lymph nodes along the pancreatic head, and in two of three lymph nodes in the para-aortic region.

Histopathologically, the tumor was diagnosed as micropapillary carcinoma of the papilla of Vater. The patient had an uneventful postoperative course and was followed up as an outpatient. Eight months after surgery, tumor recurrence with multiple liver metastasis and ascites was found, and the patient died 20 months after surgery.

Discussion

Invasive micropapillary carcinoma was originally described as a rare variant of infiltrating ductal carcinoma of the breast, with the distinctive feature of an infiltrating avascular papillary epithelial cluster. [3] This rare variant was later found arising in other organs including the urinary bladder, lung, and colon. It is associated with highly aggressive tumor behavior marked by extensive lymph node metastasis.[5-7] Invasive micropapillary carcinoma in the ampullo-pancreato-biliary region is extremely rare and its entity has not been fully described. The clinicopathological features of the IMPC in the papilla of Vater in the present case were similar to those of IMPC in the breast, with widespread metastasis in the lymphatic system, suggesting that this histological variant is nearly always associated with the propensity to invade the lymphatic system, regardless of the organ of origin. Accordingly, Khayyata et al. investigated the micropapillary pattern in carcinoma of the ampullo-pancreato-biliary region and found that tumors with a focal component of IMPC were frequently accompanied by lymph node metastasis,[8] consistent with the present case. The molecular background of IMPC has been widely investigated in breast cancer. The findings of previous studies on the mechanism of tumor metastasis and the aggressive behavior of IMPC suggest that multiple molecular pathways are responsible for the clinical features of this tumor. Some recent studies found no marked loss of E-cadherin,[9,10] but significantly higher frequency of loss of CD44 expression in IMPC of the breast.[9] The current investigation suggests that upregulation of cytoplasmic expression of stromal cell-derived factor-1 and its receptor, CXC chemokine receptor 4, might be one of the molecular mechanisms contributing to the lymph node metastasis of IMPC.[11] These findings all suggest that multiple factors contribute to the clinicopathological features of IMPC.

Only one published article has reported on the incidence of IMPC in the ampullo-pancreato-biliary region, demonstrating that 8 of 73 of periampullary carcinomas had at least one focally (>20%) invasive micropapillary component, and that frequency of tumors with a diffuse-type micropapillary pattern was exceedingly low.[8] Of the cases with at least one focal invasive micropapillary component, only 20% had an invasive micropapillary
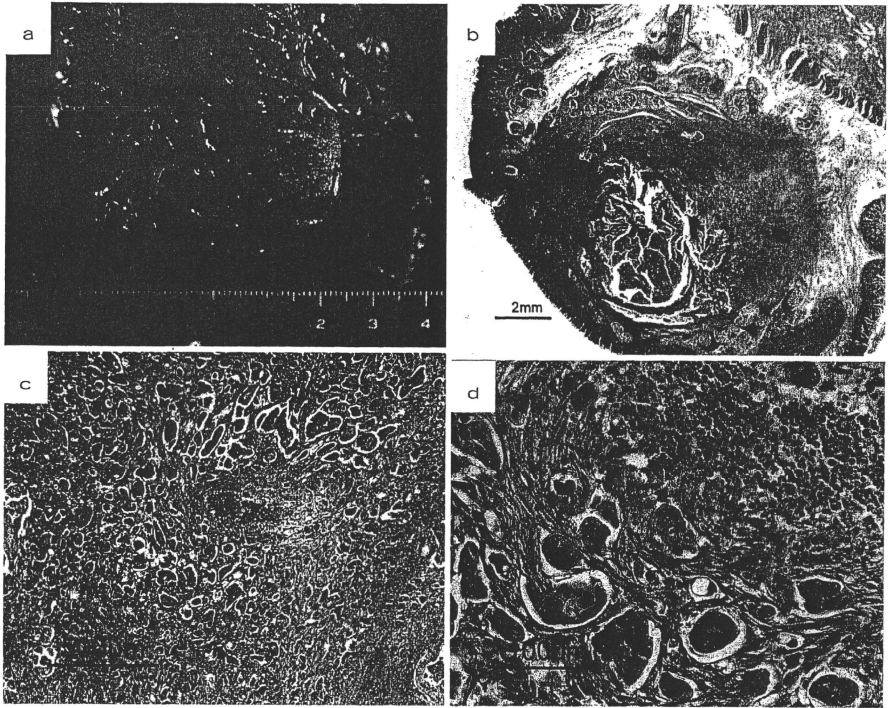
Fig. 2. **a** Macroscopic appearance of the resected specimen. A tumor with an irregular surface was observed on the papilla of Vater with obstruction of the Wirsung duct. **b** Loupe view of the resected specimen revealed that the tumor consisted of an invasive micropapillary component and a small area of a typical component of adenocarcinoma. **c** Low-power view revealed that the tumor comprised small round to ovoid micropapillary tumor cell clusters with no fibrovascular cores, lying within clefts, consistent with invasive micropapillary carcinoma of the papilla of Vater. **d** Neutrophils were identified within the stroma adjacent to the tumor cells. There was no foreign body giant cell reaction, granulation tissue, or chronic inflammation in the tumor

component as the dominant histological type.[8] We have encountered this pattern of invasive micropapillary carcinoma as the dominant component only once: in the present case, resulting in an incidence of 1.3% (1/72) among cases of papilla of Vater cancer in surgically resected specimens over the past 17 years.

Interestingly, IMPC of the ampullo-pancreato-biliary region has often been reported to be associated with tumor-infiltrating neutrophils, which is an uncommon finding of IMPC of the breast or carcinoma of this region.[8] In our case, these infiltrating neutrophils were abundant and were identified both in the area of carcinoma and in the stroma adjacent to the tumor cells. A

previous report also suggested the presence of focal microabscess in the surrounding area of the tumor cell cluster in IMPC of the ampullo-pancreato-biliary region.[8] Consistent with these observations, we found small foci of cluster of neutrophils sparsely distributed in the invasive micropapillary structure in this case (Fig. 2d). However, it has not been clarified whether tumor-infiltrating neutrophils are a specific finding of IMPC in the ampullo-pancreato-biliary region, and the clinical significance of the tumor-infiltrating neutrophils has not been identified.

The optimal treatment strategy for IMPC has not been established. With recent chemotherapeutic

advances, it is expected that adjuvant chemotherapy would result in survival benefit after the resection of pancreatic cancer. Thus, considering the aggressive tumor behavior of IMPC in the ampullo-pancreato-biliary region, adjuvant chemotherapy might be postulated for survival benefit. Indeed, adjuvant chemotherapy with gemcitabine was reported to be effective against pure invasive micropapillary carcinoma of the head of pancreas in one case report.[12] Conversely, another report suggested the potential chemotherapy-resistant character of micropapillary carcinoma,[13] concurrent with the present case, in which rapid progression of the tumor was observed despite chemotherapeutic treatment with gemcitabine. To unveil the features of IMPC in the ampullo-pancreato-biliary region, including responses to chemotherapy, further investigations with a larger number of cases are required.

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Intraductal Tubular Carcinoma of the Pancreas: Case Report with Review of Literature

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Abstract. *A 67-year-old man presented with leg edema.
Laboratory data showed elevated blood glucose and
carbohydrate antigen (CA) 19-9 levels, and anemia. Further
imaging studies revealed a relatively clear-margined tumor
totally occupying the main pancreatic duct (MPD) from the
head to the tail of the pancreas (maximum diameter 10 cm)
without mucin hypersecretion. Total pancreatectomy with
splenectomy and regional lymphadenectomy were performed.
Intraductal tubular carcinoma (ITC) was diagnosed by
immunohistochemical staining and electron microscopic
examination. Previous reports showed that this tumor is
characterized by slow growth, with a favorable prognosis
and intraductal nodular growth occupying the MPD and no
macroscopic mucus. Whether ITC should be distinguished
from other types of pancreatic neoplasm is controversial, and
the accumulation of more ITC cases and multi-institutional
analysis are necessary to establish the diagnostic criteria
and characteristics of this histological entity.*

Intraductal tubular neoplasm (ITN), with tubular architecture
or scant mucus production, has recently been described as a
variant of intraductal neoplasm of the pancreas. This type of
tumor is described in a recent Armed Forces Institute of
Pathology series (1) and in the General Rules for the Study
of Pancreatic Cancer published by the Japan Pancreas
Society (2) but not in the World Health Organization (WHO)
Classification of Tumours published by the International
Agency for Research on Cancer (IARC) (3). According to
the latest revised edition of the General Rules for the Study

of Pancreatic Cancer published by the Japan Pancreas
Society (2), ITN is classified as a subtype of intraductal
papillary-mucinous neoplasm (IPMN) (4). ITN is further
classified into intraductal tubular adenoma and intraductal
tubular carcinoma (ITC). To date, only fifteen cases of ITC
have been reported in the clinical literature (5-14).

The Authors recently encountered a case of ITC in which
it was difficult to make a decisive pathological diagnosis.

Case Report

A 67-year-old man attended a local hospital with chief
complaint of leg edema. Peripheral blood examination
revealed severe anemia (Hb: 6.4 g/dl). Gastrointestinal
endoscopy showed a duodenal tumor, and adenocarcinoma
was confirmed histologically. He was referred to our hospital
for further examinations. Physical examination revealed no
findings except for leg edema. The results of hematological,
general biochemical, and urinalysis tests were all within the
normal ranges, except for elevated blood glucose (155 mg/dl),
CA19-9 (58.3 U/ml), and anemia (Hb: 9.9 g/dl).

Gastrointestinal endoscopy showed an ulcerated tumor
with sharply demarcated margins on the wall of the
duodenum. The papilla of Vater was swollen (Figure 1).
Enhanced computed tomography (CT) detected a low density,
relatively clear-margined tumor, with maximum diameter of
10 cm in the pancreatic head. The tumor totally occupied the
main pancreatic duct (MPD) from the head to the tail of the
pancreas. The duodenum was definitely invaded by the tumor.
The tumor was close to the portal vein (Figure 2). Even with
the use of magnetic resonance (MR) imaging with MR
cholangiopancreatography (MRCP) it was not possible to
identify the MPD. Diffusion-weighted image showed a high
intensity mass in the head of the pancreas. A high intensity
tumor was also observed in the distal pancreas (Figure 3).

Based on the findings of these examinations, we made a
tentative preoperative diagnosis of acinar cell carcinoma (ACC)

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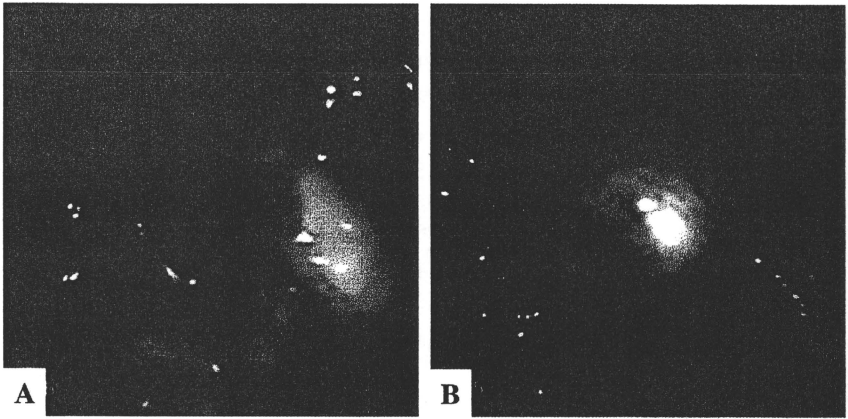*Key Words:* Intraductal tubular carcinoma, pancreas, intraductal
tubular neoplasm.

Figure 1. *Gastrointestinal endoscopy showed an ulcerated tumor with sharply demarcated, raised margins in the wall of the duodenal bulb (A). The papilla of Vater was swollen (B).*
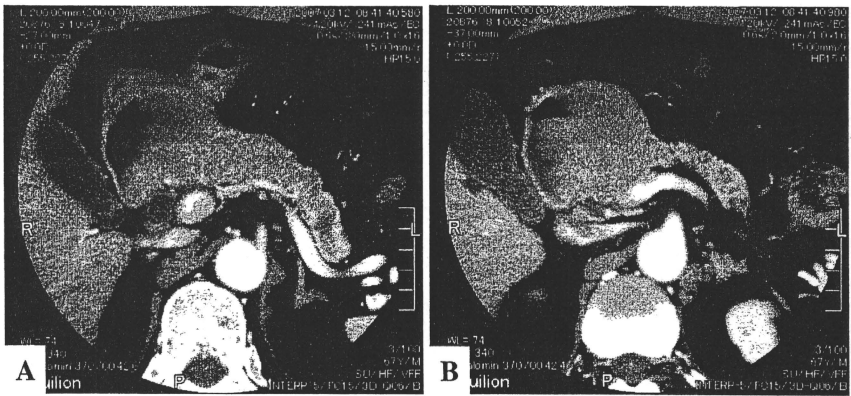

Figure 2. *Enhanced computed tomography detected a low density, relatively clear-margined tumor with maximum diameter of 10 cm in the pancreatic head. The tumor totally occupied the main pancreatic duct from the head to the tail of the pancreas. The duodenum was clearly invaded by tumor (A). The tumor was close to the portal vein (B).*

with intraductal spread of the pancreas. Total pancreatectomy with splenectomy and regional lymphadenectomy were performed. The patient's postoperative course was uneventful, and he remains alive 3 years after the operation without any symptoms or signs of tumor recurrence.

Macroscopically, the tumor was 6.5 cm in maximum diameter. The lumen of the MPD was totally filled with solid and hemorrhagic tumor. There was no mucus hypersecretion (Figure 4). The tumor was exposed to the duodenal bulb. Microscopically, the main pancreatic duct was filled with
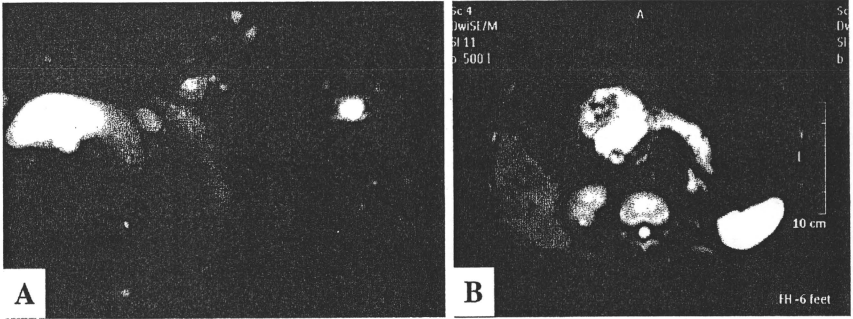
Figure 3. *Even with the use of Magnetic resonance (MR) imaging with MR cholangiopancreatography, it was not possible to identify the MPD (A). Diffusion-weighted image showed a high intensity mass in the head of the pancreas. High intensity was also observed the distal pancreas (B).*
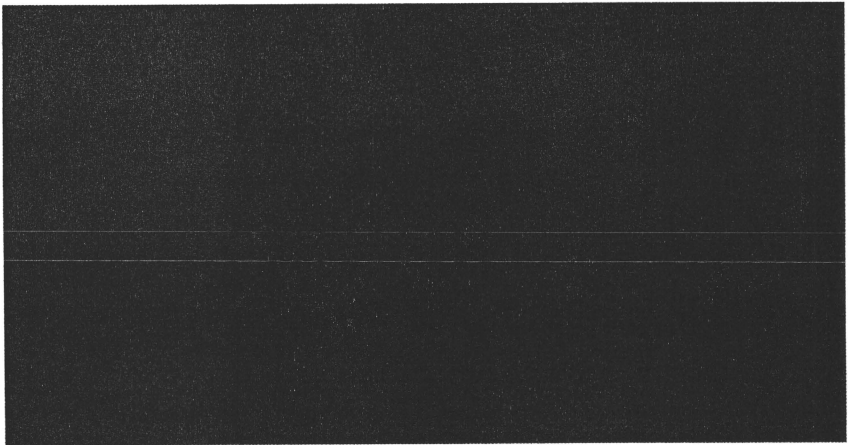

Figure 4. *Macroscopically, the tumor was 6.5 cm in maximum diameter. The lumen of the MPD was totally filled with solid and hemorrhagic tumor. There was no mucus hypersecretion.*

tumor cells, and the epithelium of most of the pancreatic duct contained atypical cells. The tumor showed small tubular structures, and tumor cells had granular and eosinophilic cytoplasm. Partially eosinophilic cells showed a sheet-like distribution. Most of the tumor was confined to the intraductal but with focal invasion to the duodenum. Periodic acid-Schiff (PAS) and diastase digestive PAS staining showed intracytoplasmic mucin secretion (Figure 5).

Immunohistochemical investigation showed the tumor cells to strongly express alpha-1-antitrypsin, cytokeratin (CK) 7, CK19, cancer antigen (CA) 19-9, and MUC1, and to weakly express amylase focally, whereas trypsin, chromogranin A, synaptophysin, cluster of differentiation (CD) 56, CK20 were not expressed (Figure 6). Electron microscopic examination did not reveal zymogen granules in the tumor cells (Figure 7). The final diagnosis was T3N1M0 stage ITC.
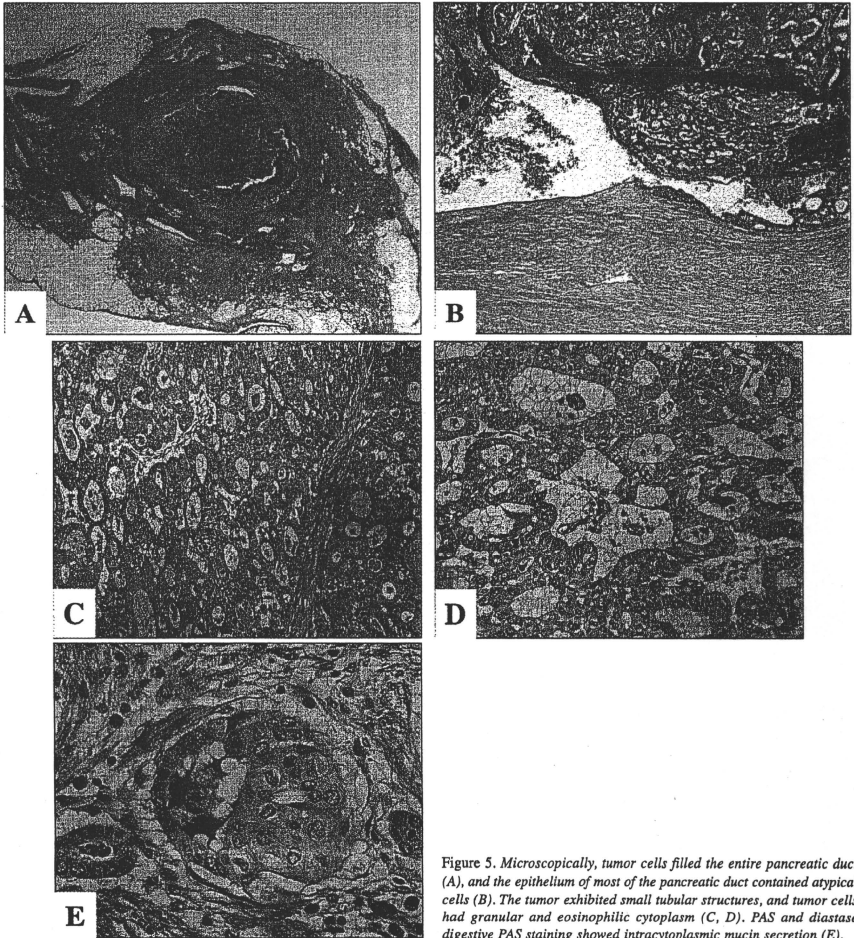
Figure 5. Microscopically, tumor cells filled the entire pancreatic duct (A), and the epithelium of most of the pancreatic duct contained atypical cells (B). The tumor exhibited small tubular structures, and tumor cells had granular and eosinophilic cytoplasm (C, D). PAS and diastase digestive PAS staining showed intracytoplasmic mucin secretion (E).

Discussion

Intraductal neoplasms of the pancreas include IPMN (4), pancreatic intraepithelial neoplasia (PanIN) (15), ITN and an intraductal variant of ACC (16-18). In this case, it was difficult to make a decisive pathological diagnosis. This case was different from ordinary IPMN or PanIN because there was a predominantly tubular neoplasm and an absence of mucus hypersecretion. Macroscopic intraductal tumors without mucus hypersecretion such as in this case, which include ACC (16-18), endocrine tumor (19, 20), and ITN, have been recently reported. This case resembled ACC in macroscopic and microscopic
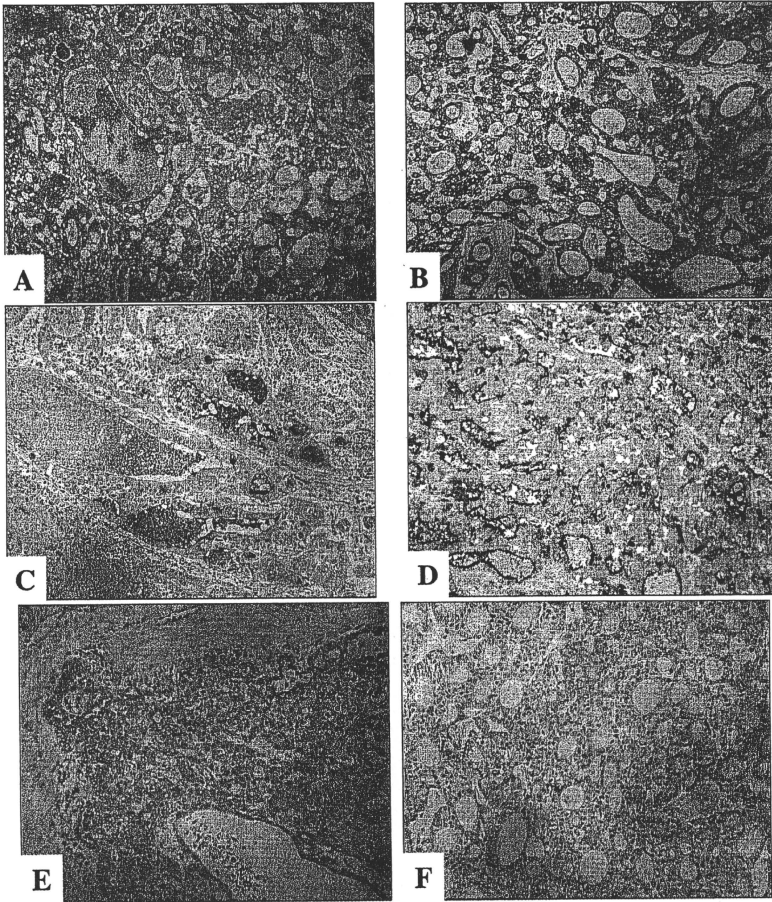
Figure 6. *Immunohistochemical investigation showed the tumor cells strongly expressed alpha-1-antitrypsin (A), CK7 (B), CA19-9 (C), and MUC1 (D), and had weak focal expression of amylase (E), whereas trypsin (F) was not expressed.*

appearance, and thus it was very difficult to differentiate it from ACC. In view of the ductal structure with intracytoplasmic mucin histologically, the expression of ductal markers CK7, CK19, and CA19-9 immunohistochemically, and the predominant intraductal spread of MUC1-positive cells, this case was diagnosed as ITC. Weak, focal expression of amylase was

seen immunohistochemically. However, electron microscopic examination did not reveal zymogen granules in the tumor cells. So this case was ultimately diagnosed as ITC.

ITC is an extremely rare pancreatic tumor that exhibits a nodular or polypoid gross appearance with a monotonous tubular growth pattern and no papillary projections or mucin

Table I. *Reported Cases of ITC.*

Authors	Age (years)	Gender	Pancreatic site	Intraductal site	Tumor size (mm)	Macroscopic mucus	Adjacent ducts	Invasion	Prognosis
Suda et al. (5)	55	M	Head	MPD	70	-	NA	Duodenum+	Alive, 7 years
Suda et al. (5)	47	M	Head	MPD	30	-	NA	Choledochus+	Dead, 5 years
Suda et al. (5)	75	F	Head	MPD	40	-	NA	Periductal+	Alive, 4 years
Suda et al. (5)	78	F	Head	MPD	30	-	NA	Periductal	NA
Ito et al. (7)	51	M	Head	MPD, Ac, Br	55×33	-	NA	-	Alive, 1 year 5 months
Tajiri et al. (8)	65	M	Head	MPD	55×16×15	-	Normal	-	Dead, 1.5 years
Tajiri et al. (8)	36	F	Body	MPD	20×10×10	-	Normal	-	Alive, 4 years
Tajiri et al. (8)	48	F	Head	MPD	26×22×30	-	Normal	-	Alive, 6 years
Tajiri et al. (8)	67	M	Tail	MPD	30×25	-	Normal	-	Dead, 2 years
Itatsu et al. (9)	50	F	Head	MPD	8×8	-	ITA	-	Alive, 23 months
Thirot-Bidault et al. (10)	67	M	Tail	MPD	30	-	Normal	-	NA
Hisa et al. (11)	84	M	Body	MPD	10×7×28	-	Normal	-	Dead, 15 months++
Oh et al. (12)	63	F	Body	MPD	25	-	Normal	-	NA
Furukawa et al. (13)	35	F	Body	MPD,Br	NA	-	NA	-	Alive, 3 years
Terada et al. (14)	67	M	Total	MPD	NA	-	ITA	-	Alive, 4 years
Present case	67	M	Total	MPD	132×65×54	-	Normal	Duodenum	Alive, 3 years

+Metastasis in lymph node; ++death due to other illness; ITC, intraductal tubular carcinoma; ITA, intraductal tubular adenoma; MPD, main pancreatic duct; Ac, accessory pancreatic duct; Br, branch pancreatic duct; NA: not available.

hypersecretion in the pancreatic ducts. Based on a MEDLINE search from 1980 through 2009, fifteen cases of ITC have been reported (5-14) (Table I). All fifteen ITC cases showed characteristics of intraductal nodular growth, occupying the MPD without macroscopic mucus hypersecretion. Suda et al. reported four cases of ITC with relatively longer survival despite invasion and metastasis to lymph nodes (5). Despite tumor invasion to the duodenum and metastasis to lymph nodes, our patient has survived for more than 28 months without any sign of recurrence. These results suggest that ITC is a slow-growing tumor with a favorable prognosis.

In summary, we had difficulty diagnosing this case precisely from morphologic findings alone. The results of immunohistochemical staining in reported cases were also not consistent (Table II). We diagnosed this case as ITC ultimately because of the findings of immunohistochemical staining and electron microscopic examination. Previous reports have suggested that this tumor is characterized by slow growth with intraductal nodular growth occupying the MPD and no macroscopic mucus, with a favorable outcome in the majority of cases. Whether ITN should be distinguished from other types of pancreatic neoplasm is controversial, and the accumulation of more ITN cases and multi-institutional analysis are necessary to establish the diagnostic criteria and characteristics of this histological entity.

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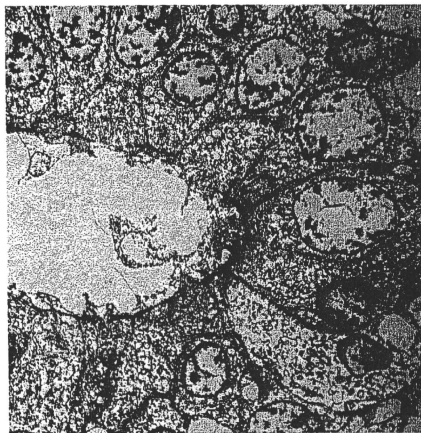

Figure 7. *Electron microscopic examination did not reveal zymogen granules in the tumor cells.*

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Table II. *Immunohistochemical data of ITC.*

Authors	PAS-AB	MUC-1	MUC-2	MUC-5AC	MUC-6	CA19-9	CEA	Dupan-2	P53	Chromogranin	Synaptophysin	Trypsin	Chymotrypsin	Amylase	Lipase
Ito *et al.* (7)									+						
Tajiri *et al.* (8)	–	+	–	–	++	–	+	–	–						
Tajiri *et al.* (8)	–	+	–	–	+	–	+	–	–						
Tajiri *et al.* (8)	–	++	–	–	–	–	+	–	–						
Tajiri *et al.* (8)	–	–	–	–	–	–	–	–	–						
Itatsu *et al.* (9)	+	–	–						+			–			–
Thirot-Bidault *et al.* (10)	+	–	–						–	–	–				–
Hisa *et al.* (11)	+	–	–		+	+	+		–						–
Oh *et al.* (12)	+	–	–						+						
Furukawa *et al.* (13)	–	–	–		+					–	–				–
Terada *et al.* (14)	–	–	+	++	++	+			+++	+	+	–	–	–	
Present case	+	++				+						–	–	–	+

ITC, Intraductal tubular carcinoma; PAS, periodic acid-Schiff staining; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; –, negative; +, <30% or partially positive; ++, >30%.

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PHYSICS CONTRIBUTION

THE DEVELOPMENT AND CLINICAL USE OF A BEAM ON-LINE PET SYSTEM MOUNTED ON A ROTATING GANTRY PORT IN PROTON THERAPY

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Purpose: To verify the usefulness of our developed beam ON-LINE positron emission tomography (PET) system mounted on a rotating gantry port (BOLPs-RGp) for dose–volume delivery-guided proton therapy (DGPT).
Methods and Materials: In the proton treatment room at our facility, a BOLPs-RGp was constructed so that a planar PET apparatus could be mounted with its field of view covering the iso-center of the beam irradiation system. Activity measurements were performed in 48 patients with tumors of the head and neck, liver, lungs, prostate, and brain. The position and intensity of the activity were measured using the BOLPs-RGp during the 200 s immediately after the proton irradiation.
Results: The daily measured activity images acquired by the BOLPs-RGp showed the proton irradiation volume in each patient. Changes in the proton-irradiated volume were indicated by differences between a reference activity image (taken at the first treatment) and the daily activity-images. In the case of head-and-neck treatment, the activity distribution changed in the areas where partial tumor reduction was observed. In the case of liver treatment, it was observed that the washout effect in necrotic tumor cells was slower than in non-necrotic tumor cells.
Conclusions: The BOLPs-RGp was developed for the DGPT. The accuracy of proton treatment was evaluated by measuring changes of daily measured activity. Information about the positron-emitting nuclei generated during proton irradiation can be used as a basis for ensuring the high accuracy of irradiation in proton treatment. © 2010 Elsevier Inc.

Dose–volume delivery guided proton therapy (DGPT), Beam ON-LINE PET system on rotating gantry port (BOLPs-RGp), Target nuclear fragment reaction.

INTRODUCTION

Proton therapy is a form of radiotherapy that enables the concentration of a dose onto a tumor by the use of a scanned or modulated Bragg peak. Therefore, it is very important to evaluate the proton-irradiated volume accurately.

Recently, to ensure the high accuracy of proton therapy, imaging studies of positron-emitting nuclei that are generated by target nuclear fragment reactions involving incident protons and nuclei from a patient's body have been performed (1–14). The annihilation gamma rays from the positron-emitting nuclei were measured by a positron emission tomography (PET) system (specifically a beam OFF-LINE PET system using commercial PET apparatus or PET-computed tomography [CT] apparatus postirradiation or a beam ON-LINE PET system in a proton treatment room). The beam OFF-LINE PET system using the commercial PET-CT apparatus has the advantage of being able to easily acquire fusion images and the ability to reconstruct three-dimensional images. However, the time required for the movement of the patient to the PET room (10–30 min) and the resulting deterioration of the statistical accuracy of the acquired data are large disadvantages. With the beam ON-LINE PET system, capturing a large view and the acquisition of three-dimensional images are difficult because of geometrical problems caused by the beam direction and the PET apparatus (7, 15, 16).

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The ability to take daily PET images with a high statistical accuracy while the patient remains in the proton irradiation room is a large advantage. Besides, availability of a cone beam (CB) CT system or CT apparatus in the irradiation room can offer the possibility of daily and in situ monitoring of the patient's anatomy. A prototype beam ON-LINE PET system (BOLPs) was previously constructed for basic research (10), and verification of the proton-irradiated volume in a patient's body was confirmed using a PET apparatus and a PET-CT apparatus (beam OFF-LINE PET system) (13).

A BOLPs mounted on a rotating gantry port (BOLPs-RGp) was constructed in our proton treatment room. Activity measurement and PET imaging were performed in 48 patients with tumors of the head and neck, liver, lungs, prostate, and brain during proton treatment at our facility. The position and intensity of the activity were measured daily using the BOLPs-RGp immediately after proton irradiation. Using the activity measurement, we were able to confirm whether the proton beam irradiation of the tumor was reproducibly performed during the treatment period. Moreover, changes in the activity distribution were observed as the volume of the tumor changed, and these changes were related to the delivery dose, changes in the body shape and position of the patient, and the physiologic changes. The PET images from the BOLPs-RGp were sufficient to provide high-quality proton treatment.

METHODS AND MATERIALS

Design of a beam ON-LINE PET system mounted on an RGp

Via the detection of pairs of annihilation gamma rays emitted from the generated radioactive nuclei of a patient's body, the BOLPs-RGp is designed to determine the position and activity of the positron-emitting nuclei generated in patients by proton irradiation. Figure 1 is a picture of the BOLPs-RGp. The BOLPs-RGp was developed as a standardized system for use with proton therapy devices. During proton therapy, the detector heads have many degrees of freedom and the system allows remote control adaptation to each new proton beam condition and a patient's position. As a result, the measurement of the activity distribution is simple.

A planar positron imaging system (Hamamatsu Photonics K. K., Hamamatsu, Japan) (17) was newly arranged for the BOLPs-RGp. In comparison to the system used previously (10), the 24 detector units mounted on each detector head were increased to 36 detector units, and each unit was composed of 11×10 arrays of BGO ($Bi_4Ge_3O_{12}$) crystals with a crystal size of $2 \times 2 \times 20$ mm^3. Furthermore, the 2,400 crystals were increased to 3,600 crystals. The gap of each unit became 3.3 mm from 11.0 mm for minimizing dead space in the detector. The field of view (FOV) became 164.8×167.0 mm^2 from 120.8×186.8 mm^2. The maximum field size is 185.0×185.0 mm^2 in the rotating gantry port with the BOLPs-RGp. Therefore, the FOV can almost cover each treatment site of the head and neck, liver, lungs, prostate, and brain for a proton treatment in our facility. However, in case of prostate, the depth activity distribution is not measured in the entrance of the incident proton beam. The BOLPs-RGp was mounted on and the center of its detection area was aligned with the iso-center of the rotating gantry in the treatment room of the proton therapy facility at our center. A PET image reconstructed by a back-projection method
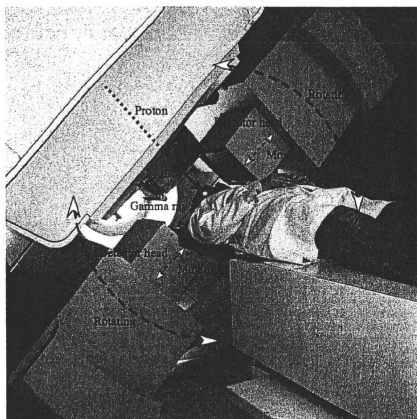

Fig. 1. Setup of the BOLPs-RGp, which is mounted on the rotating gantry port of our proton treatment room.

along the axis of the proton beam direction is always included in the FOV of the opposing detectors together with the axis of the rotating angle of the gantry system. The distance between the two opposing detector heads of the BOLPs-RGp can be adjusted from 30 to 100 cm. When the activity is not being measured, the detector head is stored inside the wall of the gantry device. The position resolution of this system is about 2 mm for the full width at half maximum in the case of use of ^{22}Na point source. The maximum data collection rate for the coincident detection of pair annihilation gamma rays is about 4,000 counts/s/cm^2 (kcps/cm^2). The accuracy of the measurements of activity distribution by this system was verified by a prototype beam ON-LINE PET system (10). The measured data are stored using in the software's list mode format. The activity image is renewed every second. The information of the on-off time points of beam irradiation is recorded in the data, and the image can be restructured according to this information. The PET data from the irradiation field of each patient are managed throughout each treatment day.

The detection efficiency of the distance between the detector heads was calibrated by using the thin-flat acrylic container filled with ^{18}F-solution. The calibration is used for a correction of the imaging uniformity and the detection sensitivity. The attenuation coefficient of 511-keV gamma rays in the patient's body was calculated by the patient's CT image data. They are used for a construction of the activity imaging. The correction of the photon scattering in the patient's body is not considered for the activity imaging. Furthermore, the photons scattered in the patient's body outside the FOV are detected by the effect of the geometry of the detector head. Therefore, the activity image is contaminated by about 10% background in this system. As the result, the position resolution of the activity distribution will become large more than 2 mm in the clinical case of a proton therapy.

Activity measurement in a patient during proton treatment

The measurement of activity was performed daily in 48 cases involving tumors of the head and neck, liver, lungs, prostate, and brain