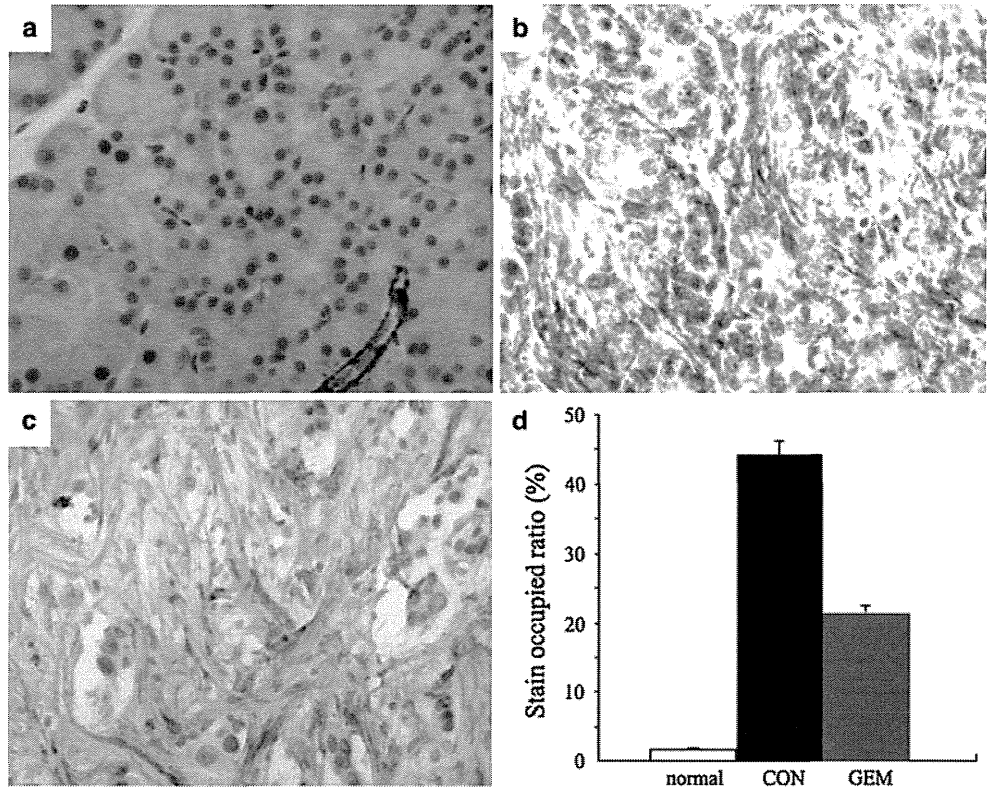

Fig. 5 Immunostaining for α-SMA of the pancreatic tissue. **a** Normal rat pancreatic tissue. **b** No treatment group (control). **c** GEM-treated group (×400). **d** Stain occupied ratio shows that α-SMA expression in pancreatic cancer tissue (*black bar*) was significantly reduced after treatment with GEM (*gray bar*) ($p = 0.03$)

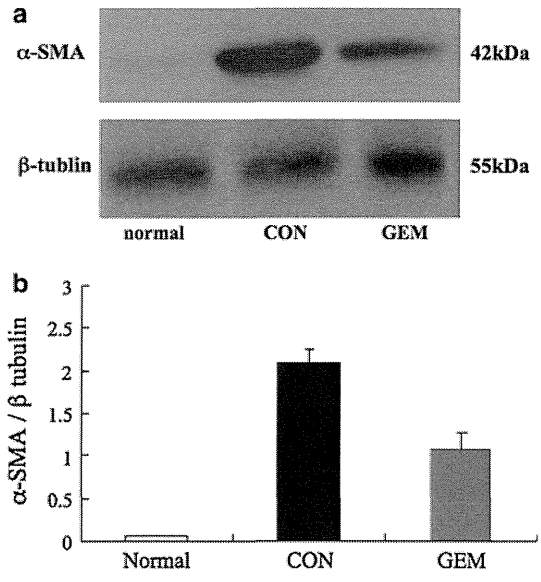

Fig. 6 Western blot analysis of α-SMA protein expression in pancreatic cancer tissue. **a** Western blot analysis of α-SMA protein. *Normal* normal rat pancreatic tissue; *CON* no treatment group (control); *GEM* GEM treated group. **b** Band intensity was quantified and expressed by ratio to β-tubulin ($n = 3$ for each group). Alpha-SMA protein of expression in pancreatic cancer tissue was significantly reduced by treatment with GEM ($p = 0.001$)

thought to migrate into the tumor from pancreatic parenchyma. Erkan et al. [16] have shown that human PSCs are practically resistant to GEM. We have been unable to discover any reports in Medline on direct GEM inhibition of rat PSC activation, but a main reason for this may be that the growth factor secretion by a tumor decreases when the growth of the tumor is being suppressed. We considered that inhibition of activation of α-SMA-positive MCs is not a direct effect of GEM.

Vascular endothelial growth factor plays an important role in tumor angiogenesis. Several reports have demonstrated that patients with pancreatic cancer showing high VEGF expression have significantly shorter survival than patients with lower VEGF expression [17–19]. In this study, we evaluated TGF-β and VEGF, which are well known growth- and PSC-activating factors secreted by pancreatic cancer cells. The expression of TGF-β was not inhibited, but VEGF expression was significantly reduced by GEM treatment. Although pancreatic cancer cells can secrete VEGF, PSCs is one of the principal sources of VEGF in pancreatic cancer tissue [20, 21]. In vitro, hypoxia increased PSC activity and doubled the secretion of periostin, type I collagen, fibronectin, and VEGF [22]. Therefore, we suggest that a decrease of VEGF expression in cancer tissue is caused by an anti-tumor effect of GEM and that inhibition of activation of α-SMA-positive MCs is a secondary effect of tumor cytokines.

Pancreatic cancer is a pathologically unique tumor that is composed of cancer cells and extremely dense desmoplasia containing ECM protein, activated PSCs, and inflammatory cells. Activated PSCs show markedly

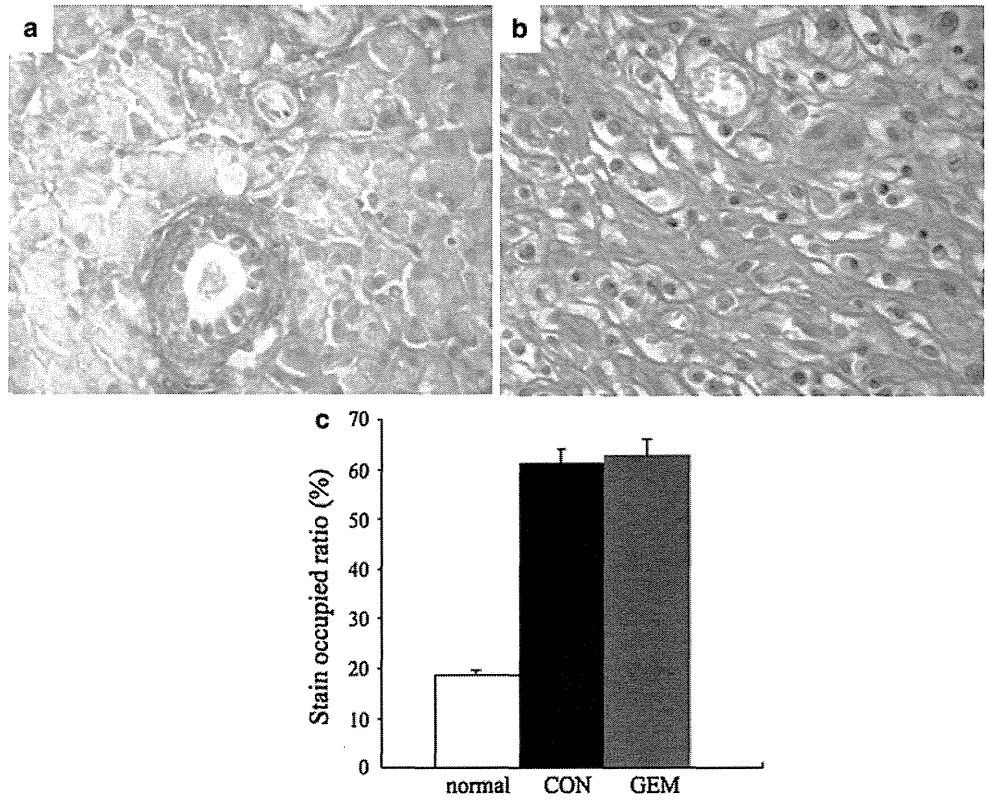

Fig. 7 Picrosirius red staining. **a** Normal pancreatic tissue. **b** Pancreatic cancer tissue (×400). **c** There was no significant difference in Picrosirius red expression in pancreatic cancer tissue between control (*black bar*) and GEM treated animals (*gray bar*)

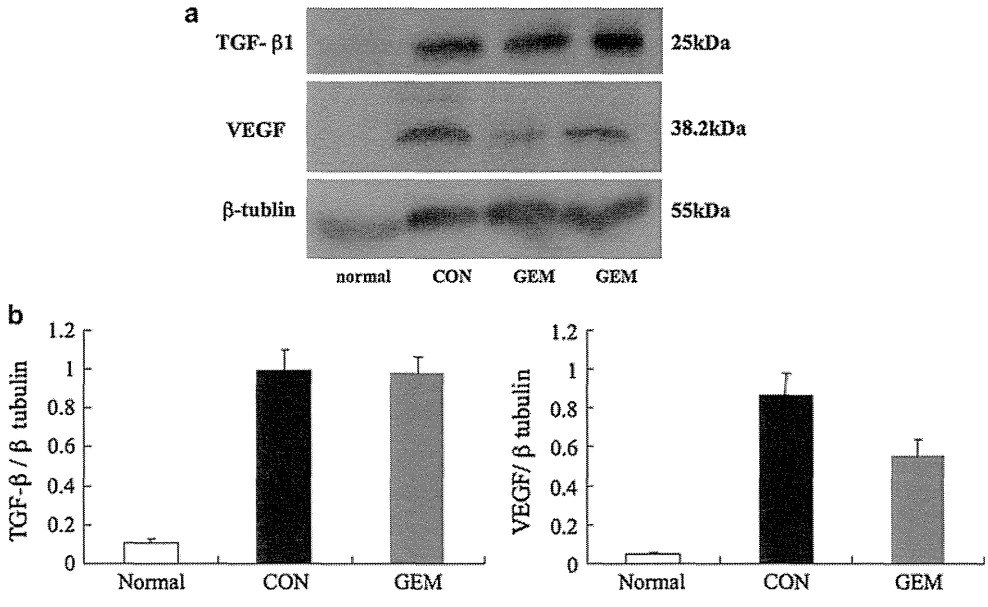

Fig. 8 Western blot analysis of VEGF and TGF-β protein expression in pancreatic cancer tissue. **a** The expression of TGF-β and VEGF in pancreatic cancer tissue. Each lane of GEM represents a different animal. *Normal* normal rat pancreatic tissue; *CON* no treatment group (control); *GEM* GEM treated group. **b** Band intensity was quantified and expressed by ratio to β-tubulin ($n = 3$ for each group). The expression of VEGF was significantly reduced by GEM treatment ($p = 0.01$), but the expression of TGF-β was not inhibited ($p = 0.41$)

increased ECM protein synthesis in response to various stimuli, such as cytokines and growth factors [5, 6], which results in pancreatic fibrosis and a hypoxic microenvironment. Our study showed that the activity of α-SMA-positive MCs in the pancreatic cancer tissue was inhibited by treatment with GEM, but the quantity of ECM did not change. Fibrosis due to chronic pancreatitis was irreversible, as shown in an earlier report [23], and also in our study. There was no change in ECM volume even if the activation of α-SMA-positive MCs, which play a pivotal role in fibrosis in pancreatic cancer tissue, was inhibited.

In summary, when pancreatic cancer growth was suppressed by GEM chemotherapy, activation of α-SMA-positive MCs in the pancreatic cancer tissue was inhibited, and the secretion of VEGF decreased but not secretion of TGF-β1. The decrease of VEGF secretion may be caused

by synergy between the suppression of the cancer cell proliferation and the suppression of activation of α-SMA-positive MCs. Even if the activity of α-SMA-positive MCs decreased, the fibrosis in the pancreatic cancer tissue was irreversible. In conclusion, GEM may not only suppress the tumor cell proliferation, but also favor the suppression of PSCs through VEGF reduction. We suggest that perhaps inhibition therapy of PSC activation in addition to chemotherapy might be a more effective strategy in pancreatic cancer treatment.

Conflict of interest None.

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and "Exact Test" produced by Prof. S. Aoki (http://aoki2.si.gunma-u.ac.jp/exact/exact.html). The χ^2 test, Fisher exact test probability, and Mann-Whitney *U* test were used as appropriate. $P \leq 0.05$ was considered as statistically significant.

RESULTS

The incidence of chyle leak was 8.0% (11/138) in all patients. The timing of start for enteral feeding was significantly earlier in the fast-track group (median, day 3; range, days 3–4) compared with the traditional group (median, day 5; range, days 3–16; $P < 0.001$). Incidence of chyle leak was significantly increased in the fast-track group compared to the traditional group (13.3% vs 1.6%, respectively, $P = 0.004$).

In comparison of clinical features, there were no significant differences between the patients with chyle leak and those without chyle leak except for early enteral feeding (timing of enteral feeding start was postoperative day 3 or 4; Table 1).

Five-day fast therapy with total parenteral nutrition was effective for all of our patients with chyle leak. No patients required the use of somatostatin analogs. Overall length of the hospital stay of the patients in the fast-track group without drain infection was significantly longer if there was a chyle leak (median hospital stay, 21 days; range, 15–28 days) compared with the patients without chyle leak (median hospital stay, 11 days; range, 5–23 days; $P < 0.001$).

DISCUSSION

In this study, we showed that the overall incidence of chyle leak in the patients who underwent DP was 8.0%. Only early enteral feeding was associated with the development of chyle leak. Chyle leak was one risk factor for prolonged hospital stay but could be successfully treated with dietary measures.

Several authors suggest lymph node dissection, neoplastic diseases, and chronic pancreatitis as risk factors for the development of chyle leak.[6–8] Malik et al[5] and van der Gaag et al[8] doubt that early enteral feeding affected the incidence of chyle leak in patients who underwent pancreatic resection (PD and DP). Our study showed that early enteral feeding was associated with chyle leak after DP.

Malik et al suggested that the mechanism of action leading to chyle leak may be due to the lipid content of the enteral feed, which may keep the visceral lymphatic channels that have been divided as part of the standard resection open, thus leading to the persistent chyle leak.[5] Chyle leak did occasionally occur despite a period of gut rest; however, it was during this period of early feeding that chyle leak became most problematic. This leads to the recognition that the likely source of this chyle was an early stimulation of the lymphatic drainage of the small intestine. Our results support this hypothesis. Our results also suggest that the visceral lymphatic channels may have remained open at least until 4 days postoperatively because all of our patients with chyle leak were started on enteral feeds on day 3 or 4.

There is little doubt that enteral nutrition carries advantages over total parenteral nutritional support. It is also easier to administer. There may be preservation of gut barrier function with enteral feeding, and it may prevent structural alterations induced by starvation and injury. However, several randomized controlled trials demonstrated that immediate postoperative enteral feeding through a jejunostomy tube is not beneficial in patients undergoing PD and is even associated with impaired respiratory mechanics and postoperative mobility.[10]

We did not deny a clinical benefit of the fast-track program for DP; however, further studies would be needed for establishing the appropriate time to start enteral feeding after pancreatic surgery.

Several authors have also shown that surgical devices such as ultrasound scissors or a vessel sealing system were not useful in preventing chyle leak.[5] In our study, we could not find benefit for using these devices in preventing chyle leak.

In conclusion, the overall incidence of chyle leak in the patients who underwent DP was 8.0% in our institute. Early enteral feeding may be associated with postoperative chyle leak. Further investigation is needed for establishing the appropriate time to start enteral feeding after DP.

The authors declare no conflict of interest.

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Long-Term Results of Surgical Resection After Preoperative Chemoradiation in Patients With Pancreatic Cancer

To the Editor:

We would like to report the long-term results of surgical resection after preoperative chemoradiation therapy (CRT) for patients with pancreatic cancer that extended beyond the pancreas.

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Pancreatic cancer is a lethal disease with poor prognosis, even in patients who have undergone resection with curative intent. Bradley[1] proposed that further improvements in the numbers of long-term survivors are unlikely to result from modifications of current surgical techniques. To achieve a 5-year survival rate exceeding 50% in patients with pancreatic cancer, Traverso[2] advocated appropriate patient selection for curative resection by accurate staging, balanced resection, centralized treatment in high-volume centers, and the use of an effective adjuvant or neoadjuvant therapy. We previously reported that preoperative CRT was able to increase the resectability rate with clear margins and to decrease the rate of metastatic lymph nodes, resulting in improved prognosis of curative cases with pancreatic cancer that extended beyond the pancreas.[3,4] Herein, we investigate actual survival results at 5 years after surgical resection after preoperative CRT for patients with pancreatic cancer that extended beyond the pancreas.

PATIENTS

Among 175 patients with a clinical diagnosis of pancreatic cancer, 87 consecutive patients with pancreatic cancer were radiologically defined as having a resectable tumor between 2000 and 2005. Among them, 68 patients underwent pancreatic resection. The preoperative CRT was performed in 35 patients who had pancreatic cancer between 2001 and 2004 as described in the previous paper.[3,4] Of these 35 patients, 27 underwent surgical resection (preoperative CRT group). Among the other 52 patients, 41 underwent surgical resection, and these were classified as the surgery-alone group comprising patients with pancreatic cancer who had a tumor limited to the pancreas (T1/T2 TNM staging) between 2001 and 2004 and the resected cases from 2000 and from 2005. From these 68 resected patients, 48 (18 in the preoperative CRT group and 30 in the surgery-only group) with residual tumor staging of R0/1 were selected. The actual 5-year survival and disease-free survival rates were compared for the following 3 groups: (1) preoperative CRT and surgery-alone groups, including unresected patients; (2) preoperative CRT and surgery-alone groups, resected patients only; and (3) preoperative CRT and surgery-alone groups, selected patients who underwent curative resection (residual tumor grading; R0/1). No patient received adjuvant chemotherapy. Informed consent was obtained from all patients according to institutional regulations, and this study was approved by the local ethics committee. Actual 5-year survival and disease-free survival rates were calculated from the start of study treatment until death or the final date of follow-up and determined by the Kaplan-Meier method. All patients had a minimum follow-up of 65 months or were observed until death. Results were considered significant at $P < 0.05$.

RESULTS

Comparisons of Actual Survival and Disease-Free Survival Rates

As shown in Figure 1A, there was no significant difference in actual survival curves between the total preoperative CRT group (n = 35) and the surgery-alone group (n = 52). The difference in 5-year survival rates between the preoperative CRT and surgery-alone groups was 17%, in favor of the former. Figure 1B shows that the actual survival curve of the preoperative CRT group comprising resected patients only (n = 27) tended to be better relative to the surgery-alone group (n = 41), although the difference (23% at 5 years) did not quite reach statistical significance ($P = 0.053$). When the patients who underwent curative resection (R0/1) were selected, there was a significant difference in the actual survival curves between the preoperative CRT group (n = 18) and surgery-alone group (n = 30; $P = 0.0228$; Fig. 1C). The difference in 5-year survival rates reached 34%. As shown in Figure 1D, a significant difference in the disease-free

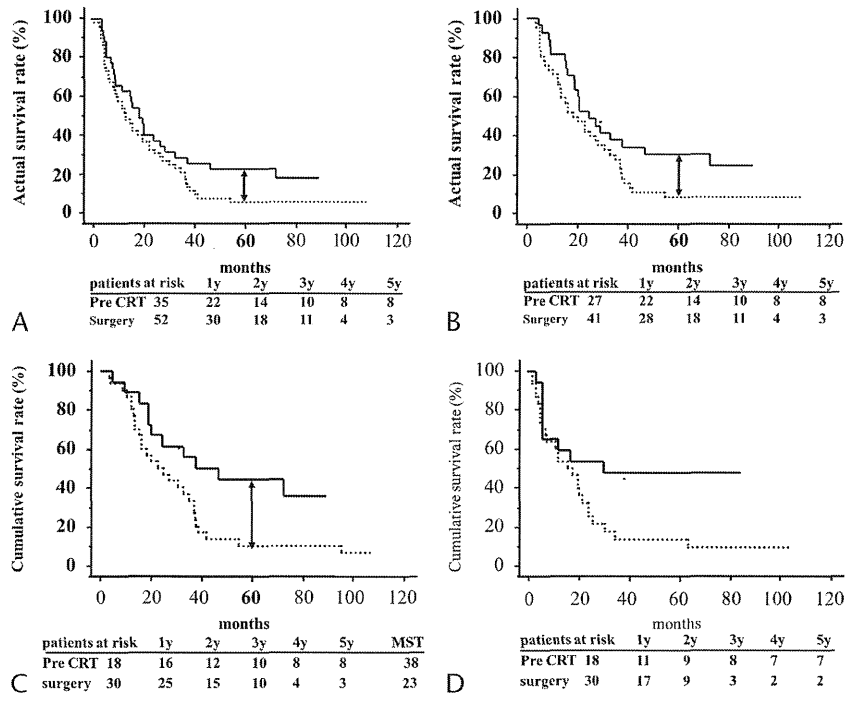

FIGURE 1. A, Actual survival curves of preoperative CRT (n = 27) and surgery-alone (n = 41) groups including unresectable patients. Solid line, preoperative CRT group; broken line, surgery-alone group. Actual survival rates at 1 year, 3 years, and 5 years were 66%, 40%, and 23% in the preoperative CRT group versus 58%, 33%, and 6% in the surgery-alone group; $P = 0.09$. The median survival time in preoperative CRT and surgery-alone groups were 19 and 13.5 months, respectively. B, Actual survival curves of the preoperative CRT and surgery-alone groups comprising resected patients. Actual survival rates at 1 year, 3 years, and 5 years were 82%, 37%, and 30% in the preoperative CRT group versus 66%, 27%, and 7% in surgery-alone groups, $P = 0.053$. The median survival time in the preoperative CRT and surgery-alone groups were 23 and 17 months, respectively. C, Actual survival curves of preoperative CRT (n = 18) and surgery-alone (n = 30) groups selecting patients who underwent curative resection. Actual survival rates at 1 year, 3 years, and 5 years were 89%, 56%, and 44% in the preoperative CRT group versus 80%, 33%, and 10% in the surgery-alone group; $P = 0.0228$. The median survival time in the preoperative CRT and surgery-alone groups were 38 and 23 months, respectively. D, Actual disease-free survival curves of the preoperative CRT and surgery-alone groups selecting patients who underwent curative resection. Actual disease-free survival rates at 1 year, 3 years, and 5 years were 61%, 44%, and 39% in the preoperative CRT group (n = 18) versus 57%, 10%, and 7% in the surgery-alone group (n = 30); $P = 0.024$.

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survival curve was also found between the 2 groups ($P = 0.024$).

Clinicopathological Features of Long-Term Survivors

Eleven patients survived longer than 5 years after surgical resection. Among them, 9 patients had negative lymph node metastasis or R0 resection. Only one patient underwent pancreatic surgery with combined resection of the celiac axis. There were 2 patients surviving with distant organ metastasis but not local recurrence at 5 years of follow-up.

DISCUSSION

In most of the patients with pancreatic cancer, the tumor is classified as unresectable at diagnosis, and only approximately 20% of patients are indicated for surgery. Even after "curative" resection, patients with pancreatic cancer face a 50% to 80% local recurrence rate and a 25% to 50% chance of developing distant metastases in the peritoneum and liver, resulting in an actual 5-year survival rate of approximately 10%.[1] Recently, some randomized studies have shown favorable results in patients with pancreatic cancer who underwent curative resection followed by adjuvant therapy, reporting median survival times within the range of 20.1 to 23.6 months.[5,6]

This retrospective study showed that actual 5-year survival rate in the preoperative CRT group comprising of R0/1 resection patients only was 44%, which was significantly superior to the 10% seen in the surgery-alone group. It is important to note that no patient received adjuvant chemotherapy, but patients with recurrent disease underwent weekly gemcitabine administration on recurrence. Bradley[1] stated that actual 5-year survival rate was only 10% in resected patients with pancreatic cancer in some studies performed between 1972 and 2002. When actual long-term patient survival rates after pancreatoduodenectomy for pancreatic cancer have been reported, they have been disappointingly lower than the optimistic survival results predicted by those studies using actuarial analysis. Since the 1980s, neoadjuvant therapy has been introduced as one of the multidisciplinary treatments for pancreatic cancer. Recently, the MD Anderson cancer center group showed that actual 5-year survival rate of patients after multidisciplinary management including surgical resection was 27%,[7] and in patients with resectable pancreatic head cancer who underwent surgical resection after preoperative gemcitabine-based chemoradiation, actual 5-year survival rate was 36%.[8] In this study, actual 5-year survival rate was 44% in patients with pancreatic cancer who underwent curative resection (R0/1). Actually, the present study demonstrated a significant difference in the actual survival curve over 3 years between the preoperative CRT and surgery-alone groups who underwent curative resection. Furthermore, there was a similar disease-free survival rate within 1 year in the preoperative CRT and surgery-alone groups in the absence of adjuvant chemotherapy, but after 1 year, the difference in the disease-free survival curve became increasingly bigger. However, approximately half of the patients who underwent curative resection had disease recurrence at 1 year and died in 2 years in both groups. Preoperative CRT followed by surgical resection did not have enough power to improve the short-term survival rate and the frequency of early liver metastases, which was one of the major postoperative recurrence sites. In this respect, addition of adjuvant chemotherapy[5,6] or targeted chemotherapy to the liver[9,10] will be expected to improve the short-term survival rate. Ohigashi et al[9] reported that the actuarial 5-year survival rate of 31 patients who underwent pancreatectomy after neoadjuvant chemoradiation therapy plus postoperative liver perfusion chemotherapy was 53%, with low incidences of both local recurrence (9%) and liver metastasis (7%). Furthermore, Sho et al[10] evaluated the efficacy of postoperative combination therapy of high-dose 5-fluorouracil arterial infusion with systemic gemcitabine in 31 patients with pancreatic cancer who underwent surgical resection, resulting in low incidence of liver metastasis (10%). Thus, postoperative adjuvant chemotherapy targeted to the liver can be associated with a beneficial effect on early hepatic recurrence.

In conclusion, preoperative CRT followed by curative resection can improve the long-term survival rate in patients with pancreatic cancer that extended beyond the pancreas. A large-scale randomized controlled trial will be needed to confirm the clinical efficacy of preoperative CRT.

The authors declare no conflict of interest.

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Utility of Contrast-Enhanced FDG-PET/CT in the Clinical Management of Pancreatic Cancer

Impact on Diagnosis, Staging, Evaluation of Treatment Response, and Detection of Recurrence

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Objectives: Fluorodeoxyglucose (FDG)–positron emission tomography/contrast-enhanced computed tomography (PET/CE-CT) involving whole-body scanning first by non–CE-CT and FDG-PET followed by CE-CT has been used for detailed examination of pancreatic lesions. We evaluated PET/CE-CT images with regard to differential diagnosis, staging, treatment response, and postoperative recurrence in pancreatic cancer.

Methods: Positron emission tomography/CE-CT was conducted in 108 patients with pancreatic cancer and in 41 patients with other pancreatic tumor diseases.

Results: The maximum standardized uptake value (SUV_{max}) overlapped in benign and malignant cases, suggesting that differential diagnosis of pancreatic tumors based on the SUV_{max} is difficult. In the evaluation of staging in 31 resectable pancreatic cancer by PET/CE-CT, the diagnostic accuracy rate was more than 80% for most factors concerning local invasion and 94% for distant metastasis but only 42% for lymph node metastasis. Significant positive correlations were found between the SUV_{max} and tumor size/markers, suggesting that SUV_{max} may be a useful indicator for the treatment response. Regarding the diagnosis of the postoperative recurrence, PET/CE-CT correctly detected local recurrence in all the 11 cases of recurrence, whereas abdominal CE-CT detected only 7 of 11 cases, suggesting that PET/CE-CT is superior in this context.

Conclusions: Positron emission tomography/CE-CT is useful for the clinical management of pancreatic cancer.

Key Words: contrast-enhanced PET/CT, differential diagnosis, clinical management, pancreatic cancer

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Despite recent significant advances in cancer diagnosis and treatment, pancreatic cancer patients still have a very poor prognosis.[1] In Japan, the number of pancreatic cancer patients in 2002 was 21,386, whereas the number of pancreatic cancer–related deaths in 2006 was 23,366,[2] indicating that the number of patients with pancreatic cancer was almost equal to the number of pancreatic cancer–related deaths. However, a slight improvement in survival has been observed with the introduction of gemcitabine and S-1 as chemotherapeutic medications for pancreatic cancer.[3,4] Given this situation, clinical practice guidelines for pancreatic cancer have recently been established in Japan, and treatment regimens are determined on the basis of the extent of pancreatic cancer, which is evaluated by imaging. contrast-enhanced abdominal CT (abdominal CE-CT) has primarily been used to determine the extent of pancreatic cancer.[5] However, imaging diagnosis is also essential in the postoperative monitoring of pancreatic cancers, which often recur soon after surgery; abdominal CE-CT imaging has also been used for this purpose.

Positron emission tomography (PET), a new imaging modality, has recently been introduced in daily clinical practice, but functional imaging by PET alone does not have much diagnostic significance.[6] Acquisition of consecutive PET and CT (PET/CT) images in addition to combination of functional PET and anatomical CT images dramatically enhances the usefulness of PET as an imaging modality.[7] We have been using PET/CT (Aquiduo 16; Toshiba, Otawara, Japan) since the introduction of this technique at the Shikoku Cancer Center in April 2006; the CT apparatus has been dedicated to dynamic studies (contrast-enhanced PET/CT [PET/CE-CT]) on the development of this technique as a key imaging modality in the diagnosis and follow-up examinations of patients with pancreatic cancer. In this study, we retrospectively compared PET/CE-CT and abdominal CE-CT, which has been used as the primary imaging modality for the diagnosis and management of pancreatic cancer, and evaluated the efficacy of these modalities for the following functions: differential diagnosis of benign and malignant pancreatic lesions, evaluation of the extent of invasive pancreatic ductal cancer, assessment of treatment effects, and diagnosis of postoperative recurrence.

MATERIALS AND METHODS

Subjects

Positron emission tomography/CE-CT imaging technology was used to determine the extent of invasive pancreatic ductal cancer in 108 patients (64 men and 44 women, aged 45–86 years). The extent of cancer was determined according to the *Classification of Pancreatic Carcinoma, Fifth Edition* (edited by the Japan Pancreas Society [JPS]).[8] Among the 108 subjects, operations were performed on 29 patients with locally advanced pancreatic ductal cancer, and histologic diagnosis was proven in these patients. The remaining patients were diagnosed on the basis of PET/CE-CT imaging findings and serum tumor marker values.

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Positron emission tomography/CE-CT imaging was conducted for relevant pancreatic tumor lesions to assess the usefulness of the maximum standardized uptake value (SUV_{max}) in differentiating benign and malignant pancreatic lesions. The SUV_{max} was the value obtained at 90 minutes after intravenous injection of fluorodeoxyglucose (FDG) in subjects with blood glucose levels of 200 mg/dL or less at the time of FDG administration.

Differential diagnosis for malignant and benign pancreatic disorders by PET/CE-CT imaging was performed in 21 patients with intraductal papillary mucinous neoplasm (IPMN; 9 men and 12 women, aged 47–78 years), in 10 patients with endocrine tumors of the pancreas (2 men and 8 women, aged 42–78 years), and in 10 patients with tumor-forming pancreatitis (chronic pancreatitis [CP] or autoimmune pancreatitis [AIP]; 8 men and 2 women, aged 40–79 years) in addition to the 108 patients with invasive pancreatic ductal cancer. Among the 21 patients with IPMN, 8 patients underwent operations, and the diagnosis of malignant tumors (intraductal papillary mucinous carcinoma [IPMC]) and benign tumors (intraductal papillary mucinous adenoma [IPMA]) was histologically proven in these patients. The remaining 13 patients were diagnosed with benign tumors (IPMA) based on the findings from imaging studies (PET/CE-CT, magnetic resonance imaging, and ultrasound), including branch type, lack of internal structures, and lack of FDG uptake. These patients are currently being observed by follow-up at more than 1 year after diagnosis. Ten patients with endocrine tumors of the pancreas were diagnosed based on the presence of hypervascular tumors with FDG accumulation on PET/CE-CT imaging. Among these patients, 7 underwent operations, and biopsies were performed in the remaining 3 patients, resulting in histologically proven diagnoses for all 10 patients. Malignancy and benignancy were determined based on histologic findings and by taking into account the presence or absence of metastatic lesions on the images. Chronic pancreatitis and AIP were diagnosed using PET/CE-CT imaging and serum levels of pancreatic enzymes and/or IgG4 according to the Diagnostic Criteria for Chronic Pancreatitis[9] 2002 and the Diagnostic Criteria for Autoimmune Pancreatitis 2006 (JPS).[10]

Classification of Pancreatic Cancer

In this study, we used the classification system for pancreatic cancer defined by the JPS.[8] According to the JPS classification system, the extent of invasive pancreatic ductal cancer was determined by taking into account local spread (T), lymph node metastases (N), and distant metastases (M). The T category was defined through determination of the presence and extent of local invasion of the pancreas and adjacent structures. Within this category, 8 local extension factors were considered: the distal bile duct (CH), duodenum (DU), serosa (S), retropancreatic tissue (RP), portal vein system (PV), arterial system (A), extrapancreatic nerve plexus (PL), and other organs (OO). The N category (lymph node metastases) was divided into 4 categories (N0-N3) according to whether metastasis was present in lymph nodes with groups 1 to 3. The presence of distant metastatic lesions, including metastasis to distant organs, the peritoneum, and group 3 lymph nodes, were defined as M1. On the basis of the grading for T, N, and M categories, tumor stage was divided into 5 groups, as shown in Fig. 1. A detailed description of stage grouping by JPS guidelines is described in a previous report by Isaji et al.[8]

PET/CT Imaging Protocol

All FDG-PET/CT studies were performed using an Aquiduo PET/CT scanner (Toshiba), which is a hybrid PET and 16-multidetector CT scanner. Patients fasted for at least 4 hours before the PET/CT examination. In all patients, blood glucose levels were checked before injection of the radiopharmaceutical. Intravenous injection of 3.0 MBq/kg body weight of FDG was followed by a 10-mL normal saline flush. Patients rested for approximately 90 minutes, during which time they were asked to drink 500 mL of a Japanese tea containing 5 mL of oral contrast medium (Gastrografin; Bayer Schering Pharma, Leverkusen, Germany) before image acquisition and to void before being positioned supine on the scanner table. Non–contrast-enhanced CT was performed first, from the vertex of the skull through the mid thigh at 80 to 200 mA s, 120 kV (peak) (kV[p]), and 2.0-mm collimation. Images were reconstructed as contiguous 4-mm slices. Positron emission tomography was performed immediately after non–contrast-enhanced CT without repositioning the patient. Positron emission tomography images were obtained at 7 to 8 stations per patient, with an acquisition time of 2 to 3 minutes per station, from the skull vertex through the mid thigh. The non–contrast-enhanced CT data were used for attenuation correction of PET emission images, which were coregistered with the non–contrast-enhanced CT data set. Then, dual-phase CE-CT was performed. Arterial-phase CT images were obtained 35 seconds after injection of 100 mL of iopamidol (Iopamiron 300; Bayer Schering Pharma). Contrast material was injected at 3 mL/s using a powder injector (Dual Shot GV; Nemoto, Tokyo, Japan). Arterial-phase images were obtained from the dome of the diaphragm to the iliac crest at 80 to 200 mA s, 120 kV(p), and 1.0-mm collimation. Arterial-phase images were reconstructed as contiguous 2-mm slices. Portal venous phase images were acquired after a delay of 90 seconds from the vertex of the skull through the mid thigh at 80 to 200 mA s, 120 kV(p), and 2.0-mm collimation. Portal venous phase images were reconstructed as contiguous 2-mm slices.

Positron emission tomography/CT imaging using this protocol (PET/CE-CT) can cover all angles of the diagnosis, including diagnosis of existing tumors, qualitative diagnosis, local diagnosis, and metastasis detection.

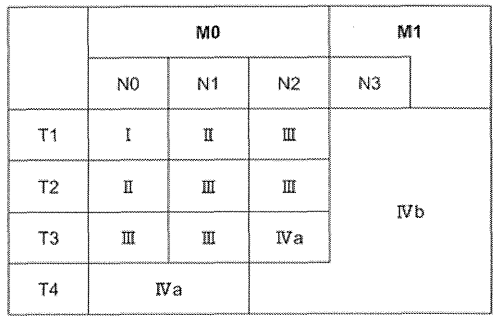

FIGURE 1. Stage grouping of pancreatic cancers according to JPS guidelines.[8] Stages of pancreatic cancer are grouped into 5 categories according to the cancer extent based on the grading of T, N, and M factors.

Evaluation of the Extent of Invasive Pancreatic Ductal Cancer

Operations were performed on 29 patients with locally advanced pancreatic ductal cancer (stage IVa), and diagnoses were histologically proven in these patients. Postoperatively, findings from PET/CE-CT imaging of the preoperative cancer were compared with the histologic findings of the resected specimens to determine the diagnostic accuracy rate of PET/CE-CT imaging for the evaluation of the extent of cancer progression. The degree of preoperative and postoperative cancer progression

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was determined according to the JPS classification system.[8] In another 4 patients with invasive pancreatic ductal cancer, whose preoperative stage was diagnosed as resectable IVa by PET/CE-CT, only metastatic tissue biopsies were performed because distant metastases were found after initiation of the surgical procedure (lymph node [N3], 2 cases; liver, 1 case; peritoneum, 1 case). Thus, N and M categories were examined in 31 patients with stage IVa after the addition of these 2 cases. We also compared the diagnostic accuracy rate of PET/CE-CT imaging with that of abdominal CE-CT imaging, which was extracted from the PET/CE-CT imaging, for evaluating the extent of cancer.

We further evaluated the diagnostic accuracy rate of PET/CE-CT for M factor analysis in 65 patients with stage IVb unresectable pancreatic cancer because distant metastases are not normally found in stage IVa resectable pancreatic cancer, and compared it with that of CE-CT images, which were extracted from the PET/CE-CT images. In this analysis, the reference standard for the presence of distant metastases was based on multimodality images and follow-up observations because distant metastases were not histologically proven.

To compare the diagnostic accuracy rates of PET/CE-CT and abdominal CE-CT in the context of evaluating T, N, and M factors, 2 radiologists were asked to analyze sections from these images independently, without knowledge of the results of the other imaging. If a disagreement occurred, a final decision was made after a discussion of the radiologists' analyses.

Assessment of Treatment Effects

The effects of treatment were evaluated over time in 8 patients who had undergone chemotherapy or chemoradiotherapy for unresectable locally advanced pancreatic cancer, diagnosed using PET/CE-CT imaging (tumor diameter determined by CT and SUV_{max} determined by PET) and serum tumor marker levels (CA 19-9). After determining the rate of increases and decreases in tumor diameter, SUV_{max} values and CA 19-9 levels were assessed, and correlations among these factors were examined. This analysis was conducted only on patients whose pancreatic cancer was locally confined during the ongoing treatment and was discontinued whenever distant metastasis occurred. At each evaluation of treatment effectiveness, the change rate of each variable was calculated and examined for correlations. Therefore, although 8 patients were analyzed, the number of analyzable events was 12 because multiple events occurred per case.

Diagnosis of Postoperative Recurrence

Although pancreatic cancer often recurs soon after surgery, the anatomical positional relationship between various abdominal organs may be changed by surgery; therefore, an abdominal CE-CT scan alone is often insufficient for diagnosis of local recurrence, not to mention distant metastasis. In the present study, PET/CE-CT images were used to show postoperative recurrence in 11 patients and a lack of postoperative recurrence of invasive pancreatic ductal cancer in 6 patients. Local recurrence was diagnosed by PET/CE-CT based on the findings of soft tissue density mass with FDG accumulation, whereas soft tissue density mass without FDG accumulation was diagnosed as a postoperative change. The diagnosis of local recurrence by abdominal CE-CT, on the other hand, requires not only the presence of soft tissue density mass but also the ability to compare the mass with the size with the previously measured mass. Thus, an increase in the size of the soft tissue density mass was considered a local recurrence, whereas no increase and/or little increase in size were considered a lack of local recurrence. However, there are no standard criteria defining the increase in size that would constitute a local recurrence; thus, the diagnosis of local recurrence depends on the radiologist. In our cancer center, PET/CE-CT is usually conducted on patients in whom the serum levels of tumor markers are elevated during the follow-up period. To determine the diagnostic accuracy rate of abdominal CE-CT for the evaluation of local recurrence, 2 radiologists were asked to read only sections from abdominal CE-CT scans extracted from PET/CE-CT imaging independently, without knowledge of the results of other imaging findings. If a disagreement occurred, a final decision was made after discussion between the radiologists. Then, the diagnostic accuracy rate for local recurrence was compared between PET/CE-CT and abdominal CE-CT imaging. Although local recurrences were not histologically proven, they were confirmed by follow-up observations after the initial diagnosis by PET/CE-CT. As a result, the diagnostic accuracy rate of PET/CE-CT was 100%.

Statistical Analysis

Differences between the SUV_{max} values in various pancreatic disorders with tumorous lesions were evaluated using the t test. Differences in the diagnostic accuracy rates of the tested imaging modalities (PET/CE-CT and abdominal CE-CT) were evaluated using the Cochran Q test. Relationships between changes in tumor size (Ts), SUV_{max} values, and serum CA 19-9 levels during treatment were evaluated using linear regression analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Differential Diagnosis of the Malignancy and Benignancy of Pancreatic Lesions by PET/CE-CT Imaging

Fig. 2 shows the SUV_{max} of various pancreatic tumor diseases. The SUV_{max} (mean [SD]) of invasive pancreatic ductal cancer was 6.14 (3.51) in stages I to III, 6.28 (2.91) in stage IVa, and 7.22 (2.65) in stage IVb; thus, the values for different stages were not significantly different. However, the SUV_{max} of invasive

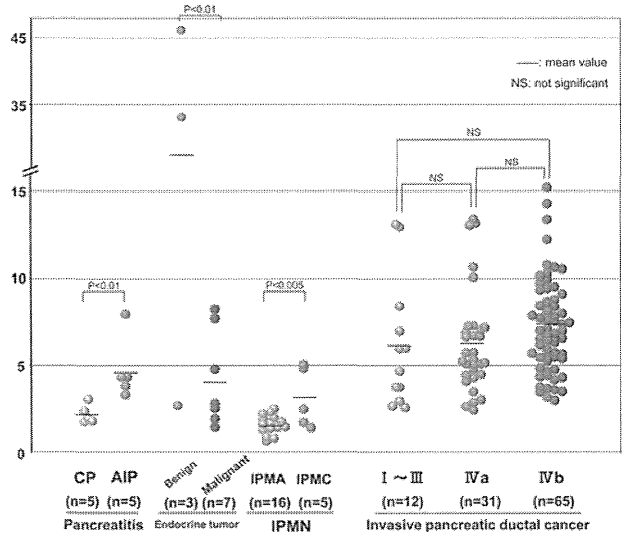

FIGURE 2. The SUV_{max} of different pancreatic tumor lesions. Ninety minutes after FDG infusion in various pancreatic tumor cases, PET/CE-CT scans were obtained to determine the SUV_{max}. Patients with blood glucose levels of 200 mg/dL or less at the time of FDG infusion were evaluated.

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pancreatic ductal cancer tended to be higher than those of other pancreatic tumor diseases, excluding benign pancreatic endocrine tumors. In the case of IPMN, the SUV_{max} values (mean [SD]) were 3.09 (1.53) for IPMC (n = 5) and 1.59 (0.52) for IPMA (n = 16). The SUV_{max} of IPMC was significantly higher than that of IPMA ($P < 0.005$). In the case of pancreatic endocrine tumors, the SUV_{max} values (mean [SD]) were 27.4 (18.2) in benign cases (n = 3) and 4.21 (2.56) in malignant cases (n = 7); thus, the SUV_{max} markedly higher in benign cases. Among 3 cases of benign endocrine tumors, 2 cases exhibited extremely high SUV_{max} values, 33.5 and 46.1, and the histologic diagnosis for these cases was well-differentiated endocrine tumor with uncertain behavior according to the World Health Organization's classification of endocrine tumors published in 2004.[11] These 2 cases have been followed up for more than 3 years, and recurrence was not noted until August 2011. In tumor-forming chronic pancreatitis (n = 5) and tumor-forming AIP (n = 5), SUV_{max} values (mean [SD]) were 2.19 (0.48) and 4.76 (1.64), respectively; therefore, the SUV_{max} of AIP was significantly higher than that of chronic pancreatitis ($P < 0.01$).

Diagnostic Accuracy Rate of PET/CE-CT Imaging for Determining the Extent of Invasive Pancreatic Ductal Cancer

The diagnostic accuracy rate of PET/CE-CT for T, N, and M factor in patients with stage IVa resectable pancreatic cancer is shown in Table 1.

With respect to the T factor, the diagnostic accuracy rate of PET/CE-CT imaging for Ts, S, and RP was below 80%, although it was greater than 80% for CH, DU, PV, A, PL, and OO. Among these factors in the T category, A, PV, and PL are important to determine whether the locally advanced pancreatic cancer (stage IVa) is resectable. The diagnostic accuracy rates of A, PV, and PL were 97%, 86%, and 83%, respectively. Evaluation of the T factor by PET/CE-CT was based on the findings of the CE-CT images; therefore, the diagnostic accuracy rate of PET/CE-CT for the T factor was identical to that of abdominal CE-CT (data not shown).

Abdominal CE-CT imaging was used to determine the extent of N factor based on the shape and size of lymph nodes, whereas FDG uptake was used as an additional evaluation element in PET/CE-CT imaging (Fig. 3). The accuracy rate of PET/CE-CT for the N factor was 42% (Table 1A), whereas that of abdominal CE-CT was 35% in 31 patients with stage IVa resectable pancreatic cancer (data not shown). The breakdown of differentially diagnosed N factor characteristics as measured by PET/CE-CT and histologic examination (n = 18) is shown in Table 1B. Among these N factor diagnoses, overestimation and underestimation of the extent of N factor characteristics by PET/CE-CT were observed in 6 and 12 patients, respectively. In the 6 cases of overestimation, 4 were determined to be stage IVb unresectable cases solely based on the preoperative evaluation of N2 or N3 by PET/CE-CT. In the 12 cases of underestimation, on the other hand, 9 with peripancreatic lymph node metastasis in the resected specimen, which is histologically diagnosed as N1, were included.

With respect to the M factor, the diagnostic accuracy rate of PET/CE-CT imaging was 94% in 31 patients with stage IVa resectable pancreatic cancer (Table 1A). Two metastatic cases, one with metastasis to the surface of the liver and the other with miliary nodules of peritoneal dissemination, were not detected by the preoperative PET/CE-CT. We also evaluated the diagnostic accuracy rate of PET/CE-CT for M factor characteristics in 65 patients with stage IVb unresectable pancreatic cancer (Table 2). Lymph node metastasis (N3), hepatic metastasis, and peritoneal dissemination, which are often observed as distant metastasis of pancreatic cancer, were detected in 51%, 55%, and 53% of patients by PET/CE-CT and 45%, 53%, and 31% of cases by abdominal CE-CT, respectively. The detection rates of abdominal CE-CT for lymph node metastasis (N3) and peritoneal dissemination were significantly lower than that of PET/CE-CT, although the detection rate of hepatic metastasis was

TABLE 1. (A) Diagnostic Accuracy Rate of PET/CE-CT Imaging in Determining the Extent of Cancer in 31 Patients With Preoperative Stage IVa Resectable Pancreatic Cancer and (B) Breakdown of the Differently Diagnosed Extent of the N Factor With PET/CE-CT Imaging and Histologic Examination in 18 of 31 Patients With Preoperative Stage IVa Resectable Pancreatic Cancer

(A) PET/CE-CT*		(B) Extent of N Factor		
		PET/CT Imaging	Histologic Examination	No. Cases (n = 18)
T factor		N3, N2	→N1	4
Ts	14/28 (50%)	N1	→N0	2
CH	24/29 (83%)	N0	→N1	9
DU	26/29 (90%)	N0	→N2	1
S	22/29 (76%)	N0	→N3	2
RP	19/29 (66%)			
PV	25/29 (86%)			
A	28/29 (97%)			
PL	24/29 (83%)			
OO	29/29 (100%)			
N factor	13/31 (42%)			
M factor	29/31 (94%)			

*The extent of cancer was determined with regard to local spread (T), lymph node metastasis (N), and distant metastasis (M) according to the classification guidelines for pancreatic carcinomas published by the JPS.[8] Preoperative cancer extent diagnosed by PET/CE-CT imaging and histologic examination of resected specimens were compared among 29 patients with stage IVa resectable pancreatic cancer to calculate the diagnostic accuracy rate of PET/CE-CT imaging. Ts was not assessable in 1 resected specimen; therefore, Ts was determined in 28 specimens. Distant metastases were histologically proven in 4 more cases (2 lymph node [N3], 1 hepatic, and 1 peritoneal metastasis), in addition to 29 patients with stage IVa resectable pancreatic cancer, in whom only tissue biopsies were performed after initiation of the surgical procedure. These 4 cases were included in N and M factor evaluation; therefore, N and M factors were histologically determined in 31 specimens.

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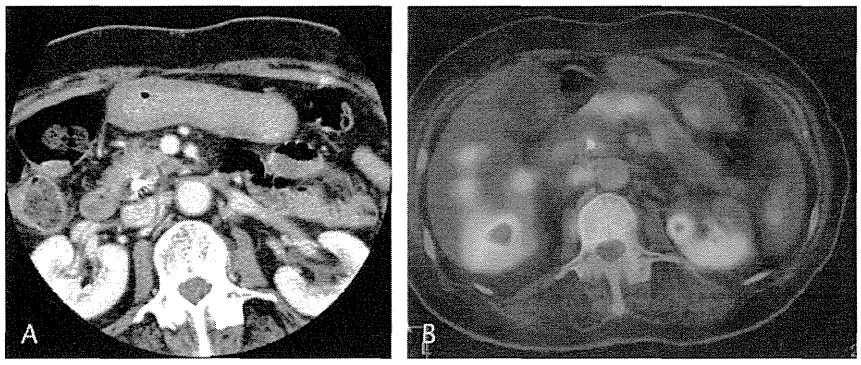

FIGURE 3. Positron emission tomography/CE-CT findings of a typical case (86-year-old woman) with lymph node metastasis. The CE-CT image shows no. 16b1 lymph node swelling (10.5 × 5.0 mm, flat shape); however, lymph node metastasis was ruled out based on the size and shape of the swelling as determined by CT (A). The PET/CT image, on the other hand, shows abnormal FDG uptake (SUV_{max}, 2.61) corresponding to this lymph node (B), suggesting lymph node metastasis. Histologic examination of the surgical specimen proved the involvement of lymph node lesions.

similar between the 2 methods. Lung and bone metastasis have rarely been detected by abdominal CE-CT because this type of imaging scans only a segmental area. Positron emission tomography/CE-CT imaging, on the other hand, scans the whole body, resulting in higher detection rates of lung and bone metastases (Table 2).

Assessment of Treatment Effects by PET/CE-CT Imaging

Unresectable pancreatic cancer is treated with chemotherapy or chemoradiotherapy, and the effectiveness of treatment is assessed according to RECIST guidelines[12] by determining the longest diameter of the measurable lesion, which is usually measured using abdominal CE-CT, and levels of serum tumor marker.

We determined the increase/decrease ratios of Ts, CA 19-9 levels, and SUV_{max} in the progressive disease and partial response groups. In contrast to small changes in Ts, the changes in CA 19-9 levels and SUV_{max} values were larger, and the patterns of changes in these indicators were similar (Fig. 4A). Among these 3 indicators, a significant positive correlation was found between SUV_{max} and CA 19-9 levels ($P < 0.0001$) and between SUV_{max} and Ts ($P < 0.05$), but no significant correlation was found between CA 19-9 levels and Ts (Fig. 4B).

TABLE 2. Difference Between PET/CE-CT and Abdominal CE-CT in the Diagnosis of the Extent of M Factor Progression in 65 Patients With Stage IVb Unresectable Pancreatic Cancer

	PET/CE-CT	Abdominal CE-CT
Lymph node (N3)	33 (51%)	29 (45%)*
Liver	36 (55%)	35 (53%)
Peritoneum	35 (53%)	20 (31%)†
Lung	12 (18%)	5 (8%)†
Bone	16 (24%)	3 (5%)†

Positron emission tomography/CE-CT was conducted at the time of diagnosis in 65 patients. The portions that correspond to the abdominal CE-CT were extracted from the PET/CE-CT images and reconstructed. Then, 2 radiologists assessed the extent of M factor characteristics on these extracted images. If a disagreement occurred, a final decision was made after discussion between the radiologists.

*$P < 0.05$ versus PET/CE-CT.

†$P < 0.01$ versus PET/CE-CT.

Diagnosis of Postoperative Recurrence

In patients with pancreatic cancer, recurrence is frequently observed shortly after the operation[13]; thus, diagnosis of recurrence is crucial for starting an appropriate treatment. Abdominal CE-CT is generally used for this diagnosis; however, in some cases, local recurrence may be difficult to detect because of postoperative alterations in the anatomical positions of visceral organs.[14,15] Therefore, we compared the rates of postoperative local recurrences diagnosed by abdominal CE-CT and PET/CE-CT imaging. Abdominal CE-CT detected 7 of the 11 cases diagnosed by PET/CE-CT imaging, and in 6 cases diagnosed as not having local recurrence by PET/CE-CT imaging, 5 cases were diagnosed correctly by abdominal CE-CT (Table 3). Typical findings from imaging of local recurrences by PET/CE-CT are shown in Fig. 5.

DISCUSSION

Preoperative evaluation of the extent of pancreatic cancer is important in deciding treatment options, and abdominal CE-CT is usually used for this purpose. In the present study, we determined the diagnostic accuracy rate of PET/CE-CT in evaluating the extent of pancreatic cancer and compared it to that of abdominal CE-CT. The accuracy rate for diagnosing the T factor, which includes an evaluation of local spread or invasion into the area surrounding the pancreas, was less than 80% for Ts, S, and RP and greater than 80% for the CH, DU, PV, A, PL, and OO. Among these factors, PV, A, and PL are important in deciding whether the tumors are resectable or not, and the accuracy rates of PET/CE-CT for these factors (PV, 86%; A, 97%; and PL, 87%) were satisfactory. The accuracy rate of abdominal CE-CT imaging for the T factor was identical to that of PET/CE-CT imaging because the CE-CT portion is the main evaluation tool for T factor analysis even on PET/CE-CT imaging. With respect to the N factor, Higashi et al[16] reported that the diagnostic accuracy rate assessed by CT images was not satisfactory. Zimny et al[17] reported a low accuracy rate for FDG-PET in evaluation of the N factor as well. In the present study, the diagnostic accuracy rate of PET/CE-CT for the N factor was 42%, despite the fact that the diagnosis was based on both CT images of the size and shape of lymph nodes and FDG uptake on PET, whereas the diagnostic accuracy rate of abdominal CE-CT was even

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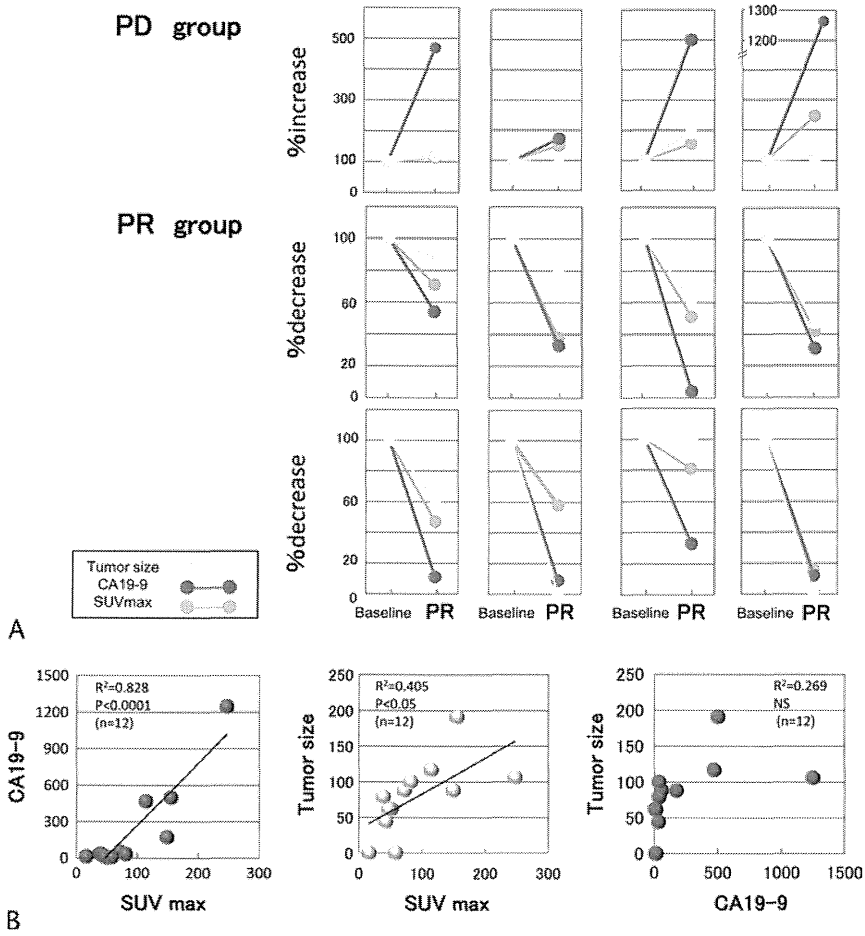

FIGURE 4. Monitoring treatment effectiveness in invasive pancreatic ductal cancer by PET/CE-CT. Chemotherapy or chemoradiotherapy was conducted in 8 patients with unresectable locally advanced pancreatic cancer. Positron emission tomography/CE-CT imaging (SUV_{max} by PET and Ts by CE-CT) and levels of serum tumor markers (CA 19-9) were used to assess the effects of treatment over time. Only tumors that were found to be locally confined during treatment were analyzed. Cases in which distant metastasis occurred were excluded from analysis. A, Changes in Ts, CA 19-9, and SUV_{max} during treatment. Compared with the baseline values (100%), the values at partial response or progressive disease are indicated by the percent decrease or increase. B, Correlations between the rate of change in Ts, CA 19-9, and SUV_{max} during treatment. NS indicates not significant.

lower (35%). The extent of the N factor was differentially diagnosed with PET/CE-CT and histologic examination in 18 cases; however, of these 18 cases, 9 cases of group 1 lymph node metastasis were diagnosed as N0 on PET/CE-CT but as N1 by histologic examination. These lymph nodes were attached to the resected specimens; therefore, detection of such lymph node metastasis by imaging seems impossible because of their small size and/or their merging with pancreatic tumors. If these 9 cases were excluded from our calculation of the diagnostic accuracy rate, the accuracy rate of PET/CE-CT for the N factor would be 13 (59%) of 22, although even this level is low. These results indicate that PET/CE-CT imaging is not very useful for assessing

TABLE 3. Positron Emission Tomography/CE-CT Versus Abdominal CE-CT for the Diagnosis of Postoperative Local Recurrence

		PET/CT	
		Recurrence (n = 11)	**No Recurrence (n = 6)**
CT	Recurrence	7	1
	No recurrence	4	5
	Accuracy rate	63%	83%

Shown are 11 cases diagnosed as "local recurrence" and 6 cases diagnosed as "no recurrence" by PET/CE-CT imaging during the postoperative monitoring period. The portion that corresponds to the abdominal CE-CT was extracted from PET/CE-CT images and reconstructed. Local recurrence was diagnosed by PET/CE-CT based on the findings of soft tissue-density mass with FDG accumulation, whereas soft tissue density mass without FDG accumulation was diagnosed as a postoperative change. The diagnosis of local recurrence by abdominal CE-CT, on the other hand, required not only the presence of soft tissue density mass but also the comparison of the current Ts with the previous measure of Ts. Two radiologists assessed local recurrence on these extracted images. If a disagreement occurred, a final decision was made after discussion between the radiologists.

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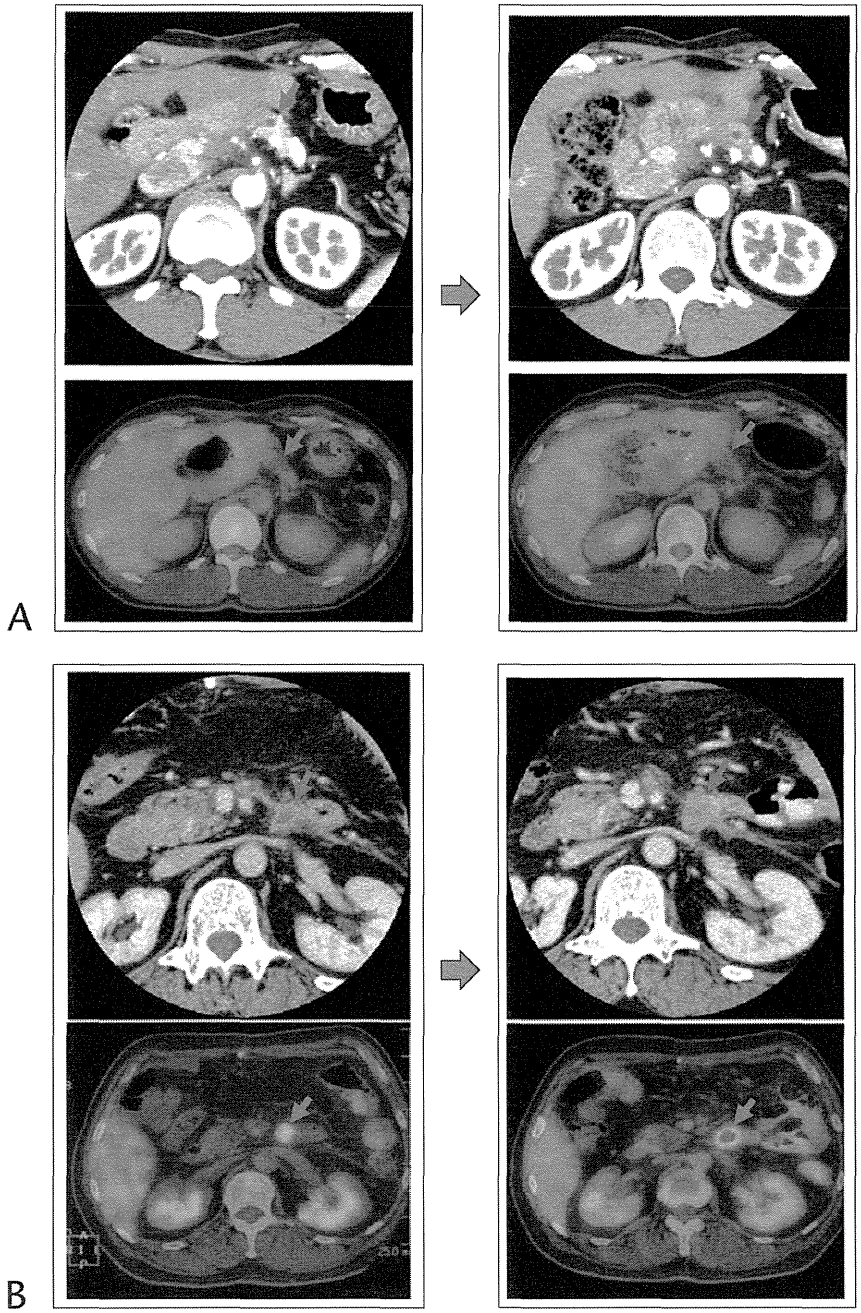

FIGURE 5. Positron emission tomography/CE-CT findings of 2 typical cases, 1 with "local recurrence" and the other with "no local recurrence," are shown. A, A 46-year-old man with no local recurrence (false-positive by CE-CT and true-negative by PET/CE-CT). The CE-CT image, which was performed 17 months after surgery, showed a soft tissue density mass, which did not rule out local recurrence (left upper panel, arrow). However, the PET/CT image did not show FDG uptake corresponding to this mass, suggesting no local recurrence (left lower panel, arrow). A follow-up PET/CE-CT image, which was performed 8 months after the initial examination, revealed no increase in the size and FDG uptake of the mass (right panel, arrow), indicating that the initial diagnosis of no local recurrence by PET/CE-CT was correct. B, A 59-year-old man with local recurrence (true-positive by CE-CT and PET/CE-CT). The CE-CT image, which was performed 3 months after surgery, showed a soft tissue density mass, which did not rule out local recurrence (left upper panel, arrow). The PET/CT image shows abnormal FDG uptake (SUV_{max}, 4.73) corresponding to this mass, suggesting local recurrence (left lower panel, arrow). A follow-up PET/CE-CT image, which was performed 3 months after the initial examination, revealed an increase in the size and FDG uptake (SUV_{max}, 6.99) of the mass (right panel, arrow), indicating that the initial diagnosis of local recurrence by PET/CE-CT was correct.

the N factor, which is consistent with previous reports.[16,17] On the other hand, PET/CE-CT is very useful in evaluation of the M factor, as indicated by the high accuracy rate of PET/CE-CT within this context. In fact, the diagnostic accuracy rate of PET/CE-CT for the M factor was 94% in 31 patients with stage IVa resectable cancers. Furthermore, in 65 patients with stage IVb

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unresectable cancers, the detection rates of PET/CE-CT for metastases to the lymph nodes (N3), liver, peritoneum, lung, and bone were 51%, 55%, 53%, 18%, and 24%, respectively. These detection rates for distant lymph node (N3) and peritoneum metastases were significantly higher for PET/CE-CT imaging than for abdominal CE-CT imaging. The detection rates of PET/CE-CT for lung and bone metastases were also higher than those of abdominal CE-CT imaging. However, such differences were attributed to the nature of PET/CE-CT scans (whole body imaging) and abdominal CE-CT scans (imaging of only a segmental area). Therefore, in the preoperative evaluation of the extent of pancreatic cancer, which is important for deciding treatment options, our present results suggest that PET/CE-CT is a useful tool for assessing T and M factors but is not very useful for assessing the N factor. This is consistent with a report by Strobel et al,[18] in which PET/CE-CT was found to be superior to PET imaging alone in assessing the respectability of pancreatic cancer.

When PET was first developed, many published reports stated that the SUV_{max} could be useful for differentially diagnosing malignancies and benignancies.[16,19] Nishiyama et al[20] and Nakamoto et al[21] reported that a malignancy could be differentiated from a benignancy in pancreatic disorders based on the SUV_{max}-to-delayed scan ratio. However, as described in the present study, the SUV_{max} of malignant pancreatic tumors overlapped with that of benign pancreatic diseases, suggesting that distinguishing between benign and malignant cases through SUV_{max}-based diagnosis is difficult. Extremely high SUV_{max} values were observed in 2 cases of benign pancreatic endocrine tumor in the present study. The SUV_{max} varies according to the several factors, including blood glucose levels, Glut 1 expression, glucose-6-phosphatase expression, and tumor heterogeneity, and others.[16] In a previous study, high SUV_{max} values were found in tumors with high Glut 1 expression.[22] In our study, extremely high SUV_{max} values were observed in 2 cases of benign endocrine tumors, and these high values may be attributed to high Glut 1 expression in these tumors; however, Glut 1 expression was not examined histologically. To differentiate between benignancy and malignancy of pancreatic tumor lesions by PET/CE-CT imaging, we first assessed the invasion of the tumors into surrounding organs/vessels and other malignancy—indicating signs by analysis of the CE-CT portion of PET/CE-CT imaging and then diagnosed the case by referring to the FDG uptake data (SUV_{max}) by analysis of the PET portion. We did not use SUV_{max} values for differentiating between benignancy and malignancy. So, what is the meaning of SUV_{max} in the clinical management of pancreatic cancer? In the present study, we examined correlations between the SUV_{max}, Ts, and tumor marker (CA 19-9) levels in unresectable locally advanced pancreatic cancer under treatment. During the course of treatment, SUV_{max} and CA 19-9 levels showed substantial positive correlations in the change rate, whereas SUV_{max} and Ts showed significant, although slight, positive correlations. However, no significant correlation was found between tumor marker levels and Ts. Treatment effects on solid tumors were assessed by determining Ts by imaging according to the RECIST criteria[12] and by the levels of serum tumor markers. In pancreatic cancer, however, changes in Ts do not necessarily reflect treatment effects because pancreatic cancers contain a variety of interstitial components. Thus, we have frequently experienced discrepancies between changes in Ts and tumor marker levels in assessing the effects of treatment, which makes it difficult to determine the effects of treatment in these cases. Identification of an additional indicator would help in determining the effects of treatment on pancreatic cancer progression/regression. In the present study, we demonstrated that the SUV_{max} measured by PET proved useful in this regard. Similarly, Yoshioka et al[23] reported that the SUV_{max} was useful to monitor the effects of treatment on pancreatic cancers. These findings, together with those in the present study, suggest that the SUV_{max} is a useful indicator for the effects of treatment on pancreatic cancer. The addition of the SUV_{max} to the existing indicators (Ts and markers) is expected to reduce the difficulty of assessing the effects of treatment on pancreatic cancer progression.

Because either invasion into the surrounding regions or distant metastasis is often already involved at the time of pancreatic cancer diagnosis, less than 20% of cases are treated surgically.[24] Even when surgery is used, recurrence usually occurs very soon thereafter.[13] Therefore, cautious observation is required after surgery. In general, abdominal CE-CT is conducted every 3 to 6 months for postoperative monitoring. Local, hepatic, and peritoneal recurrences are frequently observed postoperatively. Abdominal CE-CT can be used to diagnose hepatic recurrence, but it is sometimes difficult to detect local or peritoneal recurrences because of postoperative changes in the anatomical positions of organs.[15,17] Ruf et al[25] showed that FDG-PET is superior to CT/magnetic resonance imaging in the detection of local recurrences of pancreatic cancers. In the present study, we demonstrated that the diagnostic accuracy of PET/CE-CT is superior to abdominal CE-CT in predicting the postoperative local recurrence of pancreatic cancer. Considering the postoperative changes in the anatomical positions of abdominal organs, PET/CE-CT imaging, which uses both CE-CT and PET functions, is recommended for postoperative monitoring.

CONCLUSIONS

In the present study, we demonstrated that PET/CE-CT imaging can provide useful information in the clinical management of pancreatic cancer. We recommend PET/CE-CT imaging as the first choice examination for suspected pancreatic cancer, staging, assessment of treatment effectiveness, and confirmation of suspected recurrence.

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Diagnostic significance of a dilated orifice of the duodenal papilla in intraductal papillary mucinous neoplasm of the pancreas

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Background: A dilated orifice of the duodenal papilla found during screening endoscopy or ERCP is well-known as one of the specific findings of intraductal papillary mucinous neoplasm (IPMN). However, its clinical significance is still unclear.

Objective: To assess the diagnostic significance of a dilated orifice of the duodenal papilla and evaluate whether this could be a factor predictive of malignancy or a subtype of IPMN.

Design: Retrospective study.

Setting: University hospital.

Patients: This study involved 149 patients who underwent pancreatectomy for IPMN between January 1987 and June 2011.

Intervention: ERCP.

Main Outcome Measurements: The rate of malignant and intestinal type IPMNs in patients with and without papillary dilation.

Results: A dilated orifice of the duodenal papilla was significantly associated with intestinal type IPMN ($P < .001$), but this finding could not predict the malignant grade of IPMN ($P = .13$). Multivariate analysis revealed that a dilated orifice was a significant factor for predicting intestinal type in both main duct ($P = .01$) and branch duct IPMNs ($P < .001$).

Limitations: The validity of the definition of papillary dilation, selection bias, and a retrospective study.

Conclusion: A dilated orifice of the duodenal papilla could be a significant factor for predicting intestinal type IPMN. This may lead to better clinical management of patients with IPMN. (Gastrointest Endosc 2012;76:313-20.)

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas shows various degrees of dysplasia ranging from low, intermediate, and high-grade dysplasia to invasive carcinoma and progresses sequentially in a stepwise fashion.[1,2] In addition, IPMN also is classified into 4 subtypes including intestinal, gastric, pancreatobiliary, and oncocytic, based on the morphologic features of the mucosa and immunohistochemical findings of mucin expression.[3,4] Intestinal type IPMN shows different clinicopathologic behavior compared with the other subtypes (nonintestinal type), such as a tendency to have higher grade dysplasia but a better prognosis after resection than the nonintestinal type.[5-8] Therefore, if intestinal type IPMN could be diagnosed preoperatively and be treated with early surgical resection, then a favorable outcome would be expected.

Abbreviations: IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct.

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According to the international consensus guidelines, all main duct IPMNs are an indication for surgery, whereas surgical therapy for branch duct IPMNs remains controversial.[9-11] The size of the cyst, enlargement of the diameter of the main pancreatic duct, and the presence of symptoms or a history of acute pancreatitis are considered to be indications for surgery,[12-16] all of which appear to be derived from an increase in mucus production or viscosity. However, sensitivity to predict malignant IPMNs of each factor is not high, and, therefore, an effective indicator for determining the surgical indication for branch duct type IPMNs is urgently required.

A dilated orifice of the duodenal papilla, known as one of the classical and specific findings of IPMNs during ERCP,[17,18] is caused by mucus hyperproduction. However, its clinical significance is still unclear. Therefore, the aims of this study were to investigate the clinical significance of a dilated orifice of the duodenal papilla and to determine whether this could be a predictive factor for malignant IPMN and/or subtype of IPMN.

Take-home Message

- A dilated orifice of the duodenal papilla is a significant factor predicting intestinal type intraductal papillary mucinous neoplasms, which appear to be more frequently found with higher grades of dysplasia than nonintestinal type intraductal papillary mucinous neoplasms. Invasive cancer associated with this subtype has a better prognosis after resection, compared with that associated with the nonintestinal subtype.
- Preoperative diagnosis of intestinal subtype might be useful to shorten the surveillance interval and to recommend earlier surgical resection.

PATIENTS AND METHODS

The medical records of 183 patients who underwent surgical resection of IPMNs at the Department of Surgery and Oncology, Kyushu University, between January 1987 and June 2011 were retrospectively reviewed. Fourteen patients with concomitant pancreatic duct adenocarcinoma, 9 without detailed pathology reports, and 11 without preoperative ERCP were excluded. As a result, 149 patients were eligible. Among these patients, data from 126 patients who had undergone pancreatectomy between January 1990 and June 2009 were used in our previous studies for different purposes.[5,19-22]

The histopathologic diagnoses of IPMNs were made by 2 pathologists (K.M., S.A.) experienced in the histopathologic classification of IPMN according to the 2010 World Health Organization criteria.[2] In this study, low and intermediate grade dysplasias were regarded as nonmalignant, and high-grade dysplasia and associated invasive carcinoma were regarded as malignant, as described previously.[19] According to the subclassification proposed by Furukawa et al,[3] IPMNs were divided into 4 subtypes: intestinal, gastric, pancreatobiliary, and oncocytic. The latter 3 subtypes were further categorized as nonintestinal type. When several subtypes were observed in one patient concurrently, the histologic subclassification was determined by the subtype represented by the area of the highest degree of dysplasia of the IPMNs, as described previously.[5]

A total of 13 preoperative parameters were compared between patients who had dilated orifices of the duodenal papilla (D+) and those without dilated orifices of the duodenal papilla (D-). The parameters included sex, age (<65 years or ≥65 years), symptoms, history of acute pancreatitis, tumor location (pancreas head or body to tail), diameter of the main pancreatic duct (MPD) in branch duct type (<6 mm or ≥6 mm), size of the cyst in branch duct type (<30 mm or ≥30 mm), the presence of mural nodules, serum carcinoembryonic antigen level (normal or high; normal limit <2.3 ng/mL at our institution), serum carbohydrate antigen 19-9 level (normal or high; normal limit <37 ng/mL), morphologic type (main duct type or branch duct type), pathologic grade (nonmalignant or malignant), and subtype (intestinal type or nonintestinal type). Although the diameter of the MPD also was measured in main duct IPMNs (mean 14.2 mm; range 3.0-40 mm), this parameter was not included in the analysis because most patients (94%, 46/49) with main duct IPMNs had an MPD diameter ≥6 mm, and it could not be assessed as a possible predictive factor.

In this study, *D+* was defined as the finding that the diameter of the papillary orifice was more than twice that of a 5F catheter (more than approximately 3 mm in diameter), with mucus bulging from the orifice by visual inspection. This is classically called a "fish-eye appearance." The representative image of D+ and other related findings are shown in Figure 1. Symptoms included upper abdominal pain, back pain, appetite loss, general fatigue, and jaundice. The diagnosis of acute pancreatitis was made according to diagnostic criteria in the Japanese guidelines for the management of acute pancreatitis.[23] Acute pancreatitis associated with ERCP was excluded. US, CT, MRCP, and EUS also were performed as routine preoperative examinations to determine the tumor location, size of the cyst, diameter of the MPD, and type of IPMN. The presence or absence of mural nodules was determined by EUS. IPMN was classified into 2 types in this study: main duct type in 49 patients and branch duct type in 100 lesions, based on preoperative imaging studies. Nine mixed-type IPMNs were included in the group of main duct type IPMNs because of the similar clinicopathologic characteristics according to the Sendai guidelines. In brief, the branch duct type was defined as IPMN exclusively involv-

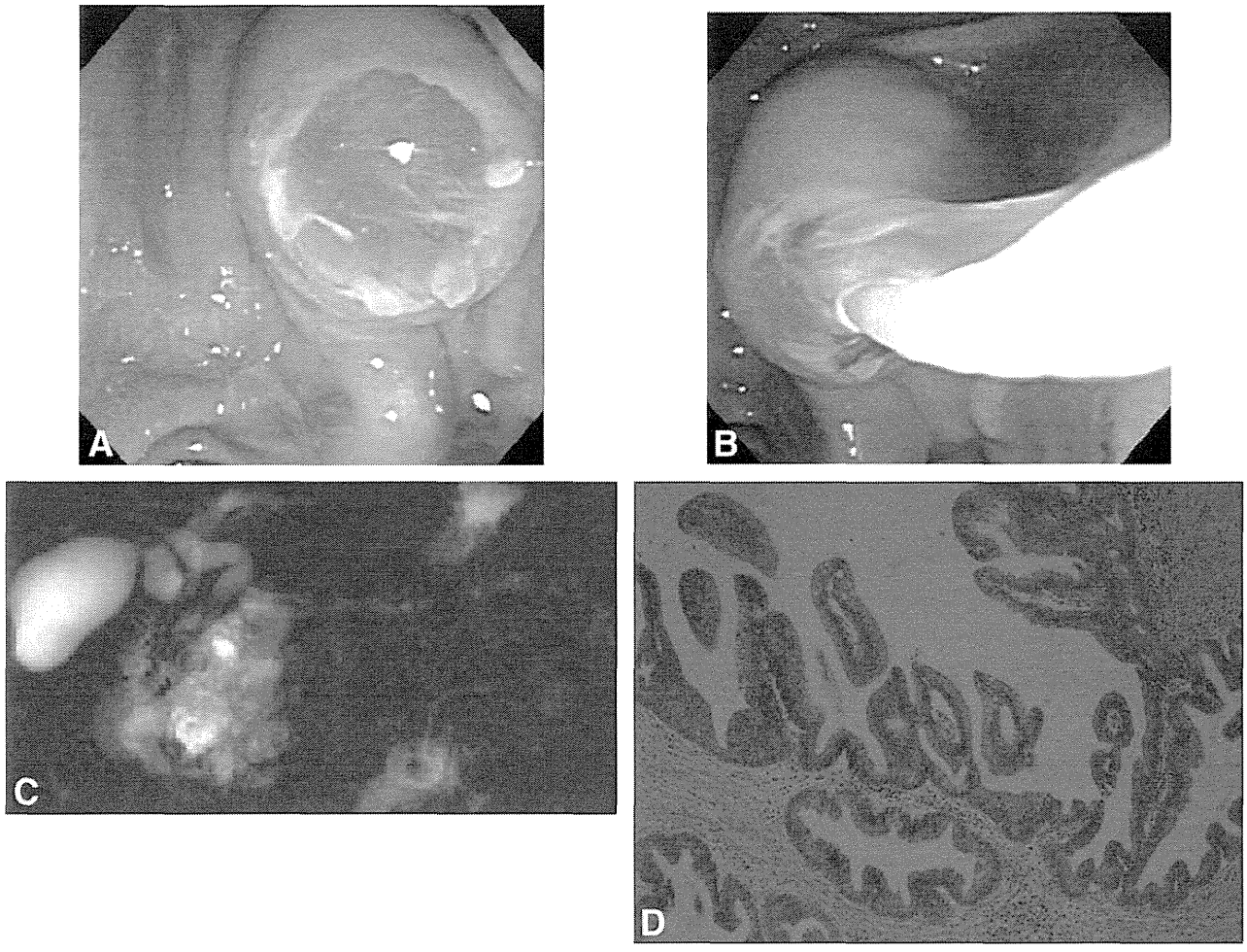

Figure 1. A, Representative finding of signs of a dilated orifice of the duodenal papilla, which is named D+ in this study. **B,** A 5F catheter is inserted into the orifice. The diameter of the orifice is twice that of the catheter, and mucus is bulging from the orifice. **C,** MRCP shows a multifocal cyst approximately 5 cm in diameter at the pancreas head. **D,** Microscopically, sections show a dilated main duct and branch ducts lined by mucinous columnar epithelium showing papillary or low-papillary growth with severe nuclear atypia. Immunohistochemically, this lesion is positive for MUC2 and MUC5AC and negative for MUC1, indicating the character of the intestinal subtype (H&E, orig. mag. ×40).

ing the branch duct and showing a grape-like collection of small cysts. The main duct type was defined as IPMN predominantly made up of dilated MPD without a grape-like appearance of the branch duct. If the IPMN had a grape-like appearance of the branch duct with dilation of the MPD but did not have findings of main duct involvement such as the presence of mural nodules in the MPD, a dilated MPD was thought to be caused by mucus hypersecretion from branch duct IPMN. Therefore, this type of IPMN was classified as the branch duct type, as previously described.[2-4]

Statistical comparisons between the 2 groups were made by the chi-square test or the Fisher exact probability test. A multivariate logistic regression model was used to investigate whether D+ was a predictive factor for a subtype of IPMNs. These statistical analyses were performed with JMP statistical software (Version 9.0.2; SAS, Inc, Cary, NC). Differences were considered to be significant if the P value was less than .05.

RESULTS

There were 76 patients in the group with a dilated papilla (D+, 51%) and 73 in the group without a dilated papilla (D-, 49%) in this study. Table 1 shows the comparative analysis of preoperative clinicopathologic characteristics between D+ and D- groups. Among 13 characters, male sex (P = .003), diameter of the MPD ≥6 mm in branch duct type (P = .013), the presence of mural nodules (P = .005), and main duct type IPMNs (P = .039) were more frequently observed in the D+ group than in the D- group. For histologic characteristics, there was no significant difference in histologic grade (P = .132) between the 2 groups, whereas D+ was significantly correlated with

TABLE 1. Comparison of clinicopathologic characteristics between IPMNs with or without papillary dilation

	Papillary dilation + (n = 76)	Papillary dilation − (n = 73)	*P* value
Sex, male/female	56/20	36/37	.003
Age, <65 y/≥65 y	31/45	26/47	.613
Symptoms, yes/no	27/49	34/39	.186
History of acute pancreatitis, yes/no	10/66	6/67	.430
Location, pancreas head/pancreas body to tail	53/23	41/32	.09
Diameter of main pancreatic duct, <6 mm/≥ 6 mm*	21/24	40/15	.013
Size of cyst, <30 mm/≥30 mm*	13/32	14/41	.822
Mural nodule, yes/no	41/35	22/51	.005
Serum CEA level, normal/high†	47/26	48/23	.727
Serum CA19-9 level, normal/high‡	65/10	59/13	.431
Main duct type IPMN/branch duct type IPMN	31/45	18/55	.039
Pathologic grade, nonmalignant/malignant	41/35	49/24	.132
Subtype, intestinal type/nonintestinal type	36/40	10/63	< .001

IPMN, Intraductal papillary mucinous neoplasm; *CEA,* carcinoembryonic antigen; *CA19-9,* carbohydrate antigen 19-9.
*Diameter of the main pancreatic duct and size of the cyst were assessed in 100 branch duct IPMNs.
†Carcinoembryonic antigen was assessed in 144 patients.
‡Carbohydrate antigen 19-9 was assessed in 147 patients.

intestinal type IPMN ($P < .001$). These results suggest that the D factor could be a preoperative factor predictive of intestinal type IPMN.

The cohort also was divided into 2 groups, the main duct type and branch duct type, because their biologic behavior is different, and the importance of predicting histologic subtype appears to be greater in branch duct IPMN than in main duct IPMN in terms of clinical management. Univariate and multivariate analyses were carried out to investigate whether the D factor could predict intestinal type IPMNs. Although a significant relationship between subtypes and the D factor was not observed in main duct IPMNs by univariate analysis ($P = .07$; Table 2), multivariate analysis revealed that D+ was a significant independent predictive factor for intestinal type IPMN (Table 3) (odds ratio [OR] 11.044; 95% confidence interval [CI], 1.620-142.906; $P = .012$). The sensitivity and specificity of the D factor for predicting intestinal type in main duct IPMNs were 80% (16/20) and 48% (14/29), respectively. On the other hand, sex ($P = .045$), history of acute pancreatitis ($P = .002$), and location (0.018) were significantly correlated with the subtypes by univariate analysis (Table 2), and the history of acute pancreatitis also was correlated with intestinal type IPMN by multivariate analysis (OR 36.320; 95% CI, 2.705-1317.469; $P = .005$) (Table 3).

In branch duct IPMNs, the frequency of intestinal type IPMN was significantly higher in the D+ group than in the D- group (45% vs 11%; $P < .001$) (Table 4). Interestingly, the prevalence of D+ was similar in the 39 branch duct IPMNs with MPD dilation (24/39 = 62%) and in the 49 MPD IPMNs (31/49 = 63%). Multivariate analysis also showed that D+ was a significant independent predictive factor for intestinal type IPMN (Table 5) (OR 17.191; 95% CI, 3.430-156.864; $P < .001$). The sensitivity and specificity of the D factor for predicting intestinal subtype in branch duct IPMNs were 77% (20/26) and 66% (49/74), respectively. Symptoms ($P = .010$) and diameter of the MPD ($P = .035$) were significantly correlated with subtypes by univariate analysis (Table 4), and symptoms also were correlated with intestinal type IPMN by multivariate analysis (OR 15.348; 95% CI, 2.766-153.952; $P = .001$) (Table 5).

We also focused on the 61 patients having branch duct IPMNs without dilation of the MPD and compared the histologic subtype and the pathologic grade between 21 patients with papillary dilation (D+) and 40 without papillary dilation (D-). The rate of intestinal subtype was significantly higher in the D+ group (8/21 patients; 38%) than in the D- group (3/40 patients; 7.5%) ($P = .005$), whereas there was no significant difference in the rate of malignancy between the 2 groups (6/21 [29%] in the D+ group and 10/40 [25%] in the D- group) ($P = .77$).

MPD involvement by papillary growth was proven by histology in 21 of 39 patients (54%) with branch duct IPMN

TABLE 2. Univariate analysis of potential factors predictive of the intestinal type in 49 main duct IPMNs

	Intestinal (n = 20)	Nonintestinal (n = 29)	*P* value
Sex, male/female	15/5	13/16	.045
Age, <65 y/≥65 y	5/15	10/19	.542
Symptoms, yes/no	12/8	13/16	.387
History of acute pancreatitis, yes/no	8/12	1/28	.002
Location, pancreas head/pancreas body to tail	7/13	21/8	.018
Mural nodule, yes/no	12/8	22/7	.345
Serum CEA level, normal/high*	10/10	17/10	.551
Serum CA19-9 level, normal/high†	17/3	21/7	.488
Orifice of duodenal papilla, dilated/not dilated	16/4	15/14	.070
Pathologic grade, nonmalignant/malignant	5/15	12/17	.361

IPMN, Intraductal papillary mucinous neoplasm; *CEA,* carcinoembryonic antigen; *CA19-9,* carbohydrate antigen 19-9.
*Carcinoembryonic antigen was assessed in 47 patients.
†Carbohydrate antigen 19-9 was assessed in 48 patients.

TABLE 3. Multivariate analysis of potential factors predictive of the intestinal type in 49 main duct IPMNs

	95% CI	OR	*P* value
Sex, male	0.130-6778	0.993	.994
Age, ≥65 y	0.174-7.560	1.138	.890
Symptom, yes	0.025-1.928	0.282	.209
History of acute pancreatitis, yes	2.705-1317.469	36.320	.005
Location, pancreas head	0.016-1.021	0.158	.053
Mural nodule, yes	0.066-3.915	0.533	.530
Serum CEA level, high	0.409-11.668	2.118	.367
Serum CA19-9 level, high	0.049-4.669	0.537	.578
Dilated orifice of duodenal papilla, yes	1.620-142.906	11.044	.012

IPMN, Intraductal papillary mucinous neoplasm; *CI,* confidence interval; *OR,* odds ratio; *CEA,* carcinoembryonic antigen; *CA19-9,* carbohydrate antigen 19-9.

with MPD dilation (≥ 6 mm) and in 17 of 61 patients (28%) with branch duct IPMN without MPD dilation (< 6 mm). The rate of MPD involvement was significantly greater in those with MPD dilation than in those without MPD dilation ($P = .012$).

The relationship between subtypes (intestinal/nonintestinal) and malignant grade (nonmalignant/malignant) also was assessed in main duct IPMNs (Table 2) and in branch duct IPMNs (Table 4). In main duct IPMNs, there was no significant difference in the rate of malignant grade between intestinal and nonintestinal types ($P = .36$). On the other hand, there was a significant relationship between the intestinal subtype and malignant grade in branch duct IPMNs ($P = .019$).

DISCUSSION

This study demonstrated that a dilated orifice of the duodenal papilla could be a significant factor predictive of intestinal type IPMNs. Although this finding cannot predict malignant IPMNs, our data have important implications for clinical management of patients with IPMNs, especially the branch duct type.

There have been several reports focusing on the factors predictive of malignant branch duct IPMNs, such as symptoms, dilation of the MPD, size of a cyst more than 30 mm, and positive pancreatic juice cytology findings; however, the sensitivity and specificity are relatively low.[12-16,25,26] We have recently reported that the combination of some