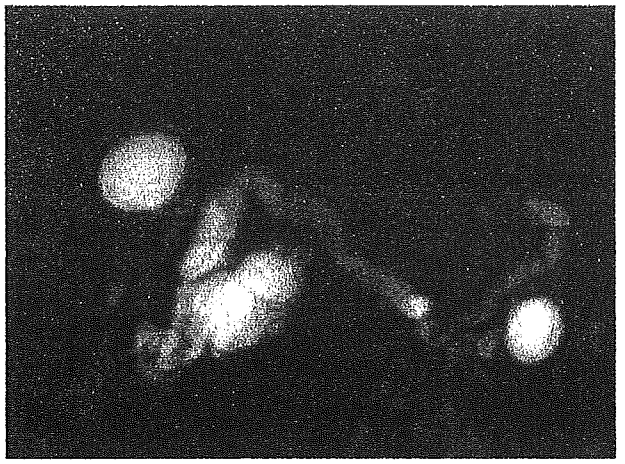

Fig. 9. MRCP outlining two branch duct IPMNs in the head and tail of the pancreas in the same patient as shown in figure 4.

suspicion of malignancy, limited resections can be planned, but should always be contingent on a careful intraoperative final assessment.

4b. Does limited resection (e.g., middle segmental pancreatectomy) have a role in surgical management of MCNs or IPMNs?

The aim of limited pancreatic resection is to preserve exocrine and endocrine pancreatic functions. Newer understanding of surgical anatomy of the pancreas has led to the proposal of various types of limited pancreatectomy [58, 59]. However, limited pancreatectomy has its problems, including technical difficulty (mostly related to a complicated surgical anatomy), a higher incidence of postoperative complications including pancreatic fistulae, and the risk of recurrence from potentially residual neoplasm. For pancreatic head lesions, duodenum-preserving pancreas head resection [60–62], pancreatic head resection with second portion duodenectomy [63], ventral pancreatectomy [64], resection of uncinate process [65], and ductal branch-oriented minimal pancreatectomy [66] have been proposed, for pancreatic body diseases, a dorsal pancreatectomy [67] and middle segmentectomy [68, 69], and for pancreatic tail neoplasms, spleen-preserving distal pancreatectomy [52–54]. Branch duct IPMNs with possible in-situ carcinoma and MCNs can be candidates for limited pancreatectomy as far as negative ductal margins can be obtained and safe pancreatectomy can be performed but no good follow-up data on recurrence are available.

4c. What should be the approach to multifocal branch duct IPMNs? In an older patient, is it reasonable to resect the portion of the gland with the largest cyst(s) alone and follow clinically to avoid total pancreatectomy?

Branch duct IPMNs can often be multifocal and located in distant segments of the pancreas (fig. 9). This is especially evident when EUS or MRCP is performed. It is unclear if multifocality confers a higher risk of invasive cancer than that predicted by the cyst size alone. If there is an indication for surgical resection (i.e., the patient is symptomatic, or the lesions are >3 cm and/or have mural nodules), a decision to proceed with a total pancreatectomy in order to remove all the lesions must be weighed carefully against the ability of the patient to manage the metabolic consequences of an apancreatic state. The age of the patient plays an important role in this decision, since the longer the life expectancy, the greater the risk of development of invasive cancer. While some studies have suggested a time lag of 5–7 years between adenomas and carcinomas (based on age differences of resected patients with benign and malignant IPMNs) [23, 24], in reality there is practically no information on the natural history of branch duct IPMNs, and it may be equally reasonable to resect the dominant lesion and observe the remainder until they become symptomatic or growth is documented.

5. Histological Questions

5a. What is the role of intraoperative frozen section consultation in the surgical management of patients with IPMNs and MCNs? In particular, should pancreatic parenchymal margins be frozen and what should be done if mucinous epithelium is identified in the larger or in the smaller pancreatic ducts?

The role of frozen section for MCNs is somewhat different from that for IPMNs:

Frozen Section for IPMNs

Frozen section of the surgical margins has an important role in the intraoperative management of IPMNs. Microscopic extension of the neoplastic cells beyond the grossly (radiologically and macroscopically) visible boundaries of the main lesion is a common occurrence in IPMNs, and this often needs to be investigated by performing a frozen section.

Caution should be exercised in interpreting the frozen section result, keeping in mind the following concerns:

(1) It should be remembered that even a negative margin does not assure the absence of neoplastic cells in the remaining pancreas. It has been well documented that IPMNs can be multifocal, and that there are sometimes 'skip' lesions in IPMNs, with non-neoplastic tissue intervening neoplastic foci. Along similar lines, there is also evidence that IPMNs may, in some instances, be a marker of invasive carcinoma [70]. This is exemplified by the cases that have an IPMN in the pancreatic head and a seemingly independent invasive ductal carcinoma in the tail of the organ. In other words, in some patients, IPMN may be a marker of a field defect and propensity for cancer formation in the pancreas, in some cases, away from the IPMN itself. Therefore, every effort should be made, preoperatively and intraoperatively, to rule out the presence of the neoplasm in the remaining pancreas. Furthermore, it has been well documented that a third of the IPMN patients have a separate malignancy in other organs [71, 72].

(2) It should also be remembered that grading of IPMNs can be subjective, and frozen tissue exhibit artifacts that accentuate the difficulty in interpretation of the histomorphologic findings. The decision to resect additional pancreatic parenchyma should be individualized and based on careful discussion between the surgeon and pathologist. A problem commonly encountered is denuded epithelium, where evaluation of the margin becomes impossible. To avoid this, gentle handling of the tissue (both in the operating room and the laboratory) is necessary. Stepwise sections of the tissue in the laboratory or even re-melting and re-embedding the reverse side of the tissue (i.e., if the fragment has not been oriented) may be considered.

Management of Positive Margins in IPMNs

The relative risk and biologic significance of various grades and subsets of IPMNs have not yet been fully established. However, the following assumptions can be made based on the current data in the literature:

IPM Adenoma. It is generally believed that IPM adenomas do not warrant further resection. This impression mostly stems from the fact that most branch duct IPMNs have been successfully followed up for decades, and only rarely developed invasive cancer. These branch duct IPMNs are typically adenomas (with no cytoarchitectural atypia) and have gastric/foveolar type epithelium, the type that used to be classified as 'IPMT (intraductal papillary-mucinous tumor) hyperplasia' in the JPS classification system [48, 73]. Whether these represent hyperplasia or adenoma is a discussion beyond the scope of this article. Regardless of the term, it is generally believed that such lesions bear only minimal risk of progression to cancer, which warrants close follow-up of the patient but does not justify (further) operation. Along the same lines, if a coincidental low-grade PanIN (1 and 2) is encountered in a resection margin, it is believed that no further resection is necessary. This impression is based on the fact that PanIN-1 and -2 are common incidental findings in the general population [40, 74].

IPMN with Borderline Atypia. This category is difficult to characterize and hence its management decision is also difficult. Not surprisingly, some of these borderline lesions are closer to adenomas and hence assumed to be less clinically significant and may not require further resection. On the other hand, those that have florid papilla formation (with villous-intestinal or pancreatobiliary patterns) may warrant further attention [75]. Typically, if there are florid papillary nodules at the margin, there are a lot more papillary nodules in the remaining pancreas, some of which prove to have higher-grade dysplasia in further examination. Therefore, such lesions may require further resection, if clinically indicated.

IPMN with CIS or Invasive Carcinoma. The relative risk of 'progression' and fatal outcome in IPMNs is difficult to calculate. Even patients with tubular type invasive carcinoma arising in IPMNs sometimes experience a more protracted clinical course than those with conventional ductal adenocarcinoma of this organ. Nevertheless, there is general consensus that IPMNs with CIS or invasive carcinoma are potentially fatal diseases if left untreated, and ought to be completely resected whenever feasible. To a lesser degree, the same may also apply to PanIN-3, which may be coincidentally encountered in patients with IPMN [76]. It should be noted that in some patients with IPMNs, it is difficult to determine whether some of the neoplastic changes within the small ducts represent PanINs or IPMNs [40, 77, 78]. At this point, this question is more an academic exercise than a practical issue, because, if such a lesion is encountered at the margin, the management should be based on the degree of cytologic atypia, and if frank CIS is noted, further resection may be attempted, if clinically indicated.

Frozen Section for MCNs

For MCNs, the role of frozen section appears to be more limited. Typically, MCNs have thick-walled cysts and their boundaries are easily discernible. The vast majority forms a localized mass in the tail or body, and unlike in IPMNs, microscopic extension of the lesion into the seemingly uninvolved pancreas is very uncommon. However, frozen section is indicated to rule out invasive

carcinoma, in particular, if a dubious firmness is close to the resection margin. If invasive carcinoma is detected at the margin, it ought to be treated as any other invasive carcinoma of this organ. Rarely, an incidental PanIN may also be detected at the margin. As discussed previously, PanIN-1 and -2 are common incidental findings, including in pancreata with MCNs [74, 79]. These are generally regarded as clinically inconsequential. Coincidental PanIN-3, on the other hand, is exceedingly uncommon in the absence of ductal adenocarcinoma. If encountered at the margin, PanIN-3 may require further attention.

5b. Are there special instructions for specimen processing in MCNs and IPMNs?

In IPMNs and MCNs, in-situ and invasive carcinoma may be multifocal and macroscopically (grossly) invisible. Therefore, it is not possible to rule out the presence of carcinoma unless the neoplasm is examined thoroughly. This is probably the main reason for the discrepancy in the literature regarding the value of grade (classification as adenoma, borderline, CIS, etc.) in these neoplasms [26, 30, 36]. It appears that undergrading due to undersampling is possibly the main reason for the 'unexpectedly' aggressive clinical course of some lower-grade examples of IPMNs and MCNs. Accordingly, some authors advocate pathologic sampling of the entire neoplasm [36, 40].

5c. Are there special instructions for specimen processing to differentiate branch duct from main duct IPMNs?

Once the neoplasm is resected and examined pathologically, the significance of classifying an IPMN as branch duct vs. main duct type is largely overridden by the other pathologic parameters such as the presence, type and extent of invasive carcinoma or grading of the IPMN component. Nevertheless, there is some evidence that branch duct IPMN may be a distinct subset, and it is suggested that the pathologists make every attempt to classify the process as branch duct or main duct type by documenting the distribution of the lesion in the ductal system. There are no special instructions for specimen processing for this purpose. However, it should be kept in mind that there are no reliable histological features to distinguish main ducts from the branch ducts in the pancreas by microscopic examination alone, especially when the duct is dilated by IPMN. Therefore, careful dissection of the specimen and proper identification of the main duct in the sections guide (either in a text form or by a diagram) is imperative in documenting the findings in the main duct. There are different approaches to dissection of these specimens, and the Japanese approach is well described in the textbook [80]. Taking a photo and a photocopy of the gross cut sections makes it easy to compare the relationships between the lesion and the main and/or branch duct.

6. Method of Follow-Up

6a. How should patients with non-resected IPMN and MCN be followed? How often should they be followed and which techniques should be employed as baseline investigations?

The decision to follow rather than resect a pancreatic cystic lesion is a matter of clinical judgment based on the age of the patient, comorbidities, and estimation of the cancer risk in the lesion. It is clear that the risk of prevalent cancer is high in main duct IPMN (table 2). Although this has not been formally studied, a review of studies on branch duct IPMN suggests that the prevalence of invasive cancer may be high (up to 30%) in symptomatic branch duct IPMN and low (0–5%) in those with asymptomatic branch duct IPMN. There are few reports in the English literature on identifying predictors of malignancy in asymptomatic mucinous lesions [22]. There have been four reports in the English literature describing the natural history of pancreatic IPMN evaluated by ERCP, CT or MRCP [81–84].

Based on limited available data from these studies it appears that asymptomatic cystic lesions without main duct dilation (>6 mm), those without mural nodules, and those <30 mm in size have a low risk of prevalent cancer and a low risk of progressing to invasive cancer in near-term (12- to 36-month) follow-up.

Ideally the imaging modality at baseline and follow-up should provide adequate information regarding the size of the lesion, size of the main pancreatic duct, and presence of intramural nodules. At least the first two criteria can be assessed satisfactorily by using non-invasive imaging studies such as multidetector high-resolution CT or MRCP, or by more invasive tests such as EUS. Assessment for intramural nodules requires EUS. Transabdominal ultrasonography is useful for follow-up in thin patients with clearly visualized cysts.

The interval between follow-up examinations remains to be determined. However, until definitive studies are performed to answer this question, it would appear reasonable to do yearly follow-up if lesion is <10 mm in size, 6–12 monthly follow-up for lesions between 10 and 20 mm, and 3–6 monthly follow-up for lesions >20 mm

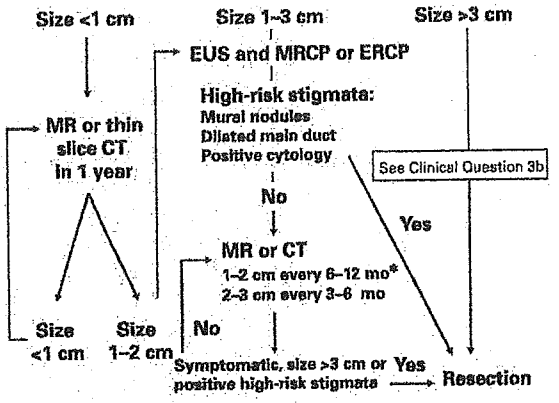

Fig. 10. Algorithm for the management of branch duct IPMN. * The interval of follow-up can be lengthened after 2 years of no change.

(fig. 10). On follow-up studies, appearance of symptoms attributable to the cyst (e.g., pancreatitis), presence of intramural nodules, cyst size >30 mm, dilation of the main pancreatic duct (>6 mm) would be indications for resection. The interval of follow-up can be lengthened after 2 years of no change.

6b. How should patients with surgically resected IPMNs and MCNs be followed? How often should they be followed and which techniques should be employed as baseline investigations?

Patients with resected benign MCNs do not need follow-up, since several studies have shown that the risk of recurrence following resection is nil [29, 35]. Patients with resected malignant MCNs do have a significant risk of recurrence, and should be followed up every 6 months regarding local recurrence and distant metastasis (mainly hematogenous) using either CT or MRI. Patients with resected benign IPMNs do have a risk of recurrence in the remaining pancreas, and if it occurs can benefit from further resection. The frequency of this event and its relationship to surgical margins (i.e., positive, negative or indeterminate) is not clear, since most series thus far have had relatively short median follow-up, but seems to be at least 7% in non-invasive IPMN [23, 24, 40]. There is no evidence in the literature to define the frequency and type of surveillance that is required to detect these recurrences. One study suggests only clinical follow-up, and imaging if symptoms appear [40], but it is not clear if imaging in absence of symptoms could be beneficial by detecting earlier lesions. It may be reasonable to get yearly follow-up with CT or MRI, and then space this interval if no changes have occurred over several years. Patients with invasive IPMNs do have a significant risk of recurrence, and probably should be evaluated every 6 months. Serum levels of CEA and CA19-9 have no proven value in the follow-up of these patients, and if obtained it should be done for the purposes of research.

6c. Should care be taken to the possible occurrence of other malignant neoplasms in patients with IPMNs on follow-up?

There have been several reports in the English literature describing the high prevalence of malignant neoplasms in patients with IPMNs but not in those with MCNs. Yamaguchi et al. [85] reported that 27% of 48 patients with IPMNs had synchronous or metachronous malignant neoplasms in the stomach, colon, rectum, lung, breast, liver, but only in 5% of 21 patients with MCNs. Sugiyama and Atomi [71] also documented that 32% of 42 patients with IPMNs developed extrapancreatic malignant neoplasms. Adsay et al. [72] found a history of another malignancy in 29% or 8 of 28 patients with IPMNs. Osanai et al. [86] gave a 24% prevalence of extrapancreatic malignancies in a large series of 148 patients with IPMNs. Furthermore, Yamaguchi et al. [70] reported synchronous or metachronous occurrence of pancreatic cancer of ordinary type in the pancreas harboring IPMNs. Although there is not yet definitive evidence, care should be taken to the possible occurrence of malignant neoplasms in the pancreas and other organs in patients with IPMNs on follow-up.

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GASTROENTEROLOGY

Small carcinoma of the pancreas is curable: New computed tomography finding, pathological study and postoperative results from a single institute

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Abstract

Background: It is well known that pancreatic cancer is rarely cured and is usually fatal. The clinicopathological features of small (greatest dimension ≤2 cm by histologic measurement) carcinoma of the pancreas (s-PC), were reviewed, paying special attention to new computed tomography (CT) finding that suggests the presence of s-PC.

Methodology: Sixteen patients with s-PC have undergone curative surgery at Aichi Cancer Center Hospital during the past 11 years. Their preoperative diagnostic findings, pathological findings and postoperative prognoses were analyzed.

Results: The most useful diagnostic clue was dilatation of the main pancreatic duct (MPD). It was difficult to identify the tumor in four patients because of pancreatitis accompanying the MPD obstruction. In three of these four cases, early phase-enhanced CT revealed a contrasting effect between the proximal and distal sides of the pancreatic parenchyma at the site of the MPD obstruction (black & white sign). The longest diameters of the tumors ranged from 0.9 to 2 cm (average 1.3 cm). Positive rates of capsular invasion, retroperitoneal invasion, and lymph node metastasis were 6.3% (1/16), 31.3% (5/16), and 18.8% (3/16), respectively. Six patients (37.5%) were classed at stage I, six (37.5%) stage II, three (18.8%) stage III, and one (6.2%) at stage IV according to pathological TNM classification. One patient died of the disease, and the cumulative 3- and 5-year survival rates were 88.9% and 59.3%, respectively.

Conclusions: The presence of s-PC qualifies as early PC and has a good prognosis. The CT black + white sign will be useful in the diagnosis of s-PC accompanying pancreatitis.

Key words: black & white sign on CT, early pancreatic cancer, histologic tumor size, small pancreatic cancer.

INTRODUCTION

Early symptoms of invasive ductal carcinoma of the pancreas (PC) are uncharacteristic, making the disease difficult to diagnose, and postoperative prognosis for PC is generally poor.[1–4] It is generally believed that the smaller the tumor, the earlier the clinical stage, with the chance of a curative outcome being greater for a small tumor than a large tumor.[2,5–7] In the present retrospective study we reviewed the clinicopathological features and postoperative results of patients who had undergone curative surgery for small carcinoma of the pancreas (s-PC; greatest dimension ≤2 cm by histological measurement). Special attention was paid to new computed tomography (CT) finding that suggests the presence of s-PC.

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METHODS

From January 1992 to December 2002, 70 patients underwent surgical resection of PC at the Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan. Intraductal papillary tumors, ampullary carcinomas and islet cell tumors were excluded. Sixteen of 70 patients with PC were diagnosed as having s-PC. During this period, there was no s-PC that was not resected curatively because of metastases or gross invasion. The patients' reasons for consultation, preoperative diagnostic findings, surgical procedures, pathological findings and postoperative prognoses were analyzed in detail.

The whole tumor was sectioned continuously and carefully examined macroscopically. The cut surfaces were processed in entirety for histopathologic examination, using the slice through the lesion. Blocks for processing were fixed in 10% formalin and embedded in paraffin. Microscopic sections were stained with hematoxylin and eosin. Tumor size was determined by histologic measurement. Capsular invasion, retroperitoneal invasion, invasion to the peripancreatic tissues, and metastasis to the regional lymph node were histologically evaluated. All patients were staged according to the International Union Against Cancer (UICC) system.[8] In this study, tumor (T) and nodal (N) factors were determined by histopathologic findings of the resected specimens (pathological TNM classification).[8]

The cumulative survival rate was calculated by the Kaplan–Meier method. The log–rank test was used to evaluate differences between survival curves.

RESULTS

The patients were eight men and eight women, ranging in age from 42 to 82 years (mean 65.2 years) at the time of surgical resection. Eight patients (50%) had symptoms or signs at the time of diagnosis: abdominal pain in six patients and jaundice in two (Table 1). The remaining eight patients had no symptoms; their tumors were detected on preoperative or postoperative examination of carcinoma of another organ in five patients, and medical check up in three.

Ultrasonography, endoscopic ultrasonography, CT and endoscopic retrograde pancreatography in all patients revealed obstruction and/or dilatation of the main pancreatic duct (MPD) in the tail of the pancreas (Table 2). Pancreatic tumor was detected in 12 patients, but obscured by pancreatitis accompanying the MPD obstruction in the other four. In three of these four patients, early phase-enhanced CT revealed a contrasting effect between the proximal and distal sides of the MPD obstruction (Fig. 1). This was not the case in the 12 patients whose tumor was identified, and in 54 patients whose tumor size was > 2 cm. During the same period (1992–2002) 93 patients underwent pancreatic resection for cystic tumor of the pancreas, islet cell tumor and pancreatitis, but no patient showed this finding on CT.

The tumor was located in the head of the pancreas in 10 patients and in the body in the remaining six. Pancreaticoduodenectomy was performed in nine, pylorus-preserving pancreaticoduodenectomy in one and distal pancreatectomy in six patients. We dissected group 1 and 2 lymph nodes given in the *General Rules for Cancer of the Pancreas* of the Japan Pancreatic Society.[9] Eleven patients, whose tumor was strongly suspected of PC on

Table 1 Reason for consultation

	No. patients	%
Symptom and/or signs	8	50
Abdominal pain	(6)	
Jaundice	(2)	
Pre- or postoperative examination of other diseases	5	31
Gastric cancer	(2)	
Colon cancer	(2)	
Lung cancer	(1)	
Medical check up	3	19
Total	16	100

Table 2 Diagnostic findings on various modalities

	No. patients	%
Obstruction and/or dilatation of MPD	16	100
Detection of the tumor	12	75

MPD, main pancreatic duct.

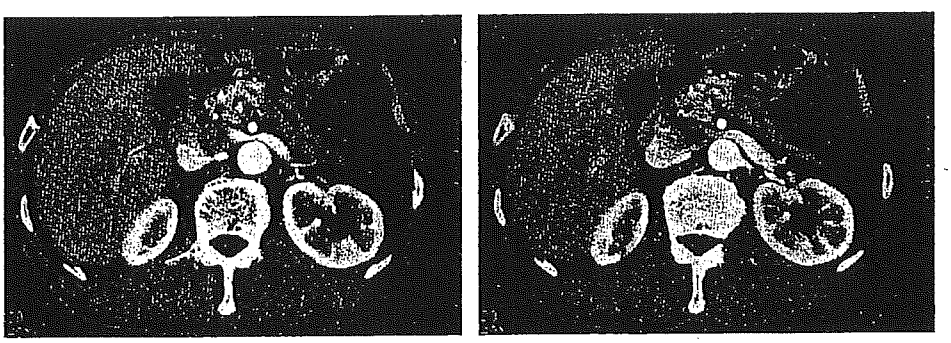

Figure 1 Black & white sign on computed tomograph (CT; Table 3, case 7). There was a contrasting effect between the proximal and distal sides of the pancreatic parenchyma at the site of main pancreatic duct (MPD) obstruction. The boundary was extremely clear.

Table 3 Pathological findings and outcome

Case	Size (cm)	Histological grading	S	RP	CH	DU	T	N	M	Stage	Recurrence	Follow up (months)
1	2.0	G2	(−)	(−)	(+)	(+)	3	1	0	III	(−)	105, AW
2	1.0	G2	(−)	(−)	(−)	(−)	1	0	0	I	(−)	98, AW
3	2.0	G2	(−)	(−)	(+)	(+)	3	0	0	II	(−)	61, DOOD
4	1.5	G2	(−)	(+)	(−)	(−)	3	0	0	II	(−)	57, AW
5	0.9	G2	(−)	(−)	(+)	(−)	3	0	0	II	(−)	48, AW
6	1.3	G2	(−)	(−)	(−)	(−)	1	0	0	I	(−)	43, AW
7	1.0	G2	(−)	(−)	(−)	(−)	1	1	0	III	(−)	38, AW
8	1.9	G2	(−)	(−)	(−)	(−)	1	0	0	I	(−)	35, AW
9	1.5	G2	(−)	(+)	(−)	(−)	4	0	0	IVa	(+)	28, DOD
10	0.9	G2	(+)	(+)	(−)	(−)	3	0	0	II	(−)	23, AW
11	2.0	G2	(−)	(+)	(−)	(−)	3	0	0	II	(−)	18, AW
12	1.2	G2	(−)	(−)	(−)	(−)	1	0	0	I	(−)	15, AW
13	1.5	G1	(−)	(−)	(−)	(−)	1	1	0	III	(−)	14, AW
14	1.0	G2	(−)	(−)	(−)	(−)	1	0	0	I	(−)	14, AW
15	1.2	G2	(−)	(−)	(−)	(−)	1	0	0	I	(−)	5, AW
16	1.2	G1	(−)	(+)	(−)	(−)	3	0	0	II	(−)	3, AW

AW, alive and well; CH, invasion of the common bile duct; DOD, died of disease; DOOD, died of other disease; DU, invasion of the duodenum; G1, well differentiated tubular adenocarcinoma; G2, moderately differentiated tubular adenocarinoma; N, regional lymph node metastasis; RP, retroperitoneal in vasion; S, capsular invasion; T, primary tumor.

preoperative diagnostic findings, underwent intraoperative radiation therapy (IORT); radiation doses from 25 to 35 Gy, with electron beam energies between 6 and 16 MeV, were delivered.

Histopathological evaluation of the 16 resected specimens showed tumor sizes ranging from 0.9 to 2 cm (average 1.3 cm). All were found to be ductal adenocarcinoma: well differentiated in two patients and moderately differentiated in 14 (Table 3). Positive rates of capsular invasion, retroperitoneal invasion, and lymph node metastasis were 6.3% (1/16), 31.3% (5/16), and 18.8% (3/16), respectively. Six patients (37.5%) were classified as being in stage I, six (37.5%) in stage II, three (18.8%) in stage III, and one (6.2%) in stage IV.

One patient died of the disease 28 months after resection, one died of other causes after 61 months and 14 remained alive without tumor recurrence after 3–105 months.

The cumulative 3- and 5-year survival rates for s-PC were 88.9% and 59.3%, respectively. Rates for patients with PC > 2 cm were significantly lower (18.7% and 9.3%, respectively; $P < 0.0001$; Fig. 2).

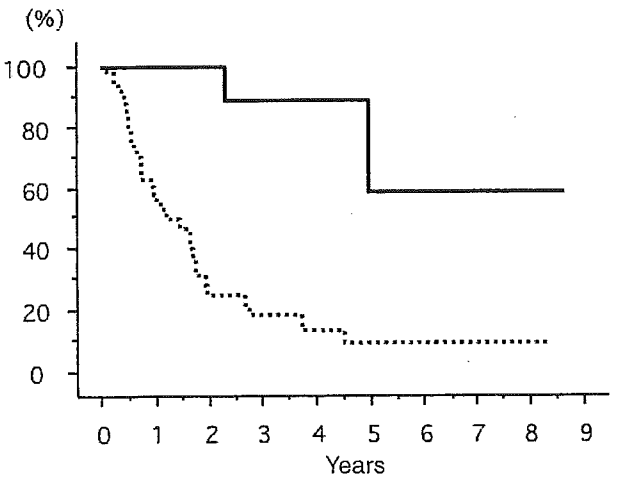

Figure 2 Cumulative survival rates after resection of pancreatic carcinoma. Kaplan–Meier survival curves for 16 patients with tumors ≤2.0 cm (—) and 54 with tumors >2.0 cm (····). The survival difference was significant ($P < 0.0001$).

DISCUSSION

It is well known that pancreatic cancer is rarely cured and is often fatal.[1] Because there are no characteristic symptoms or effective medical check for the disease, it is difficult to diagnose at an early stage. In the many reviews of surgical treatment of pancreatic carcinoma, the overall 5-year survival rate was around 10%.[2,3,10,11] To our knowledge, there are few reports of s-PC.[7,11–18] To determine whether small, probably early cancers represent the curable condition, we reviewed the clinicopathological features and postoperative results of patients who underwent curative surgery for s-PC.

Eight of the patients (50%) consulted a doctor with some symptoms. The other eight patients' pancreatic abnormalities were incidentally noted on imaging procedures during medical check up or examination of other diseases. The most useful clue for diagnosis of s-PC was MPD dilatation. It was difficult to identify the tumor in four patients (Table 3, cases 7, 8, 12, 13) because of pancreatitis accompanying MPD obstruction, but early phase-enhanced CT revealed a contrasting effect between the proximal and distal sides of the obstruction in three of these four cases (cases 7, 8, 12).

It seems to be the mirror of an underlining pancreatitis, but the boundary was extremely clear (Fig. 1). This is a sign of segmental obstruction of MPD in the normal pancreas. During the same period (1992–2002) 93 patients underwent pancreatic resection for cystic tumor, islet cell tumor and pancreatitis, but no patient had this sign. We regard this as a new and important finding that suggests the presence of s-PC, and name it 'the black & white sign'.

Even with s-PC, the invasive nature was apparent in the resected specimen. The fact that 25% of the patients were classified as being in stage III or IV indicates that it is necessary to adequately remove regional lymph nodes and soft tissue adjacent to the pancreas. Fortunately 15 patients classified as being in stage I, II or III remained alive without tumor recurrence except one who died of other causes. The patient whose tumor involved the splenic vein, classified as being in stage IV (Table 3, case 9) died of the disease 28 months after resection.

A 5-year survival rate of approximately 35% in patients with s-PC, ≤2 cm in greatest dimension, is reported in the literature.[7,11–13,15–18] There are some collective studies, but only very few reports from a single institution, in which diagnoses, operations and pathological examinations follow uniform principles.[11–13,15,17] The overall survival rate of the present patients (5-year survival 59%) was greater than those in the Tsuchiya *et al.* collective report,[12] in which 1-, 3-, and 5-year survival rates were 77.8%, 44.5%, and 30.3%, respectively. The reason for this difference is not clear; but tumor size was measured macroscopically in the Tsuchiya *et al.* series and histologically in the present case. Further, eight of the present 16 patients had T1 tumors (Table 3), which were also limited to the pancreas, and 11 patients underwent IORT, which may prevent local recurrence,[19–22] in addition to resection.

Taken together, our findings show that carcinoma of the pancreas, which is one of the worst cancers in terms of curability and prognosis, has a good prognosis if resected when the tumor diameter is ≤2 cm. It is reasonable to consider these small lesions as early PC, and further investigations and efforts in their detection should be made. The black & white sign on CT will be useful in the diagnosis of s-PC accompanying pancreatitis.

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GASTROENTEROLOGY

Late complication in patients undergoing pancreatic resection with intraoperative radiation therapy: Gastrointestinal bleeding with occlusion of the portal system

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Abstract

Background: There are few reports of late complications in patients who have undergone pancreatic resection with intraoperative radiation therapy (IORT), because carcinoma of the pancreas (PCa) and the bile duct (BCa) have a poor prognosis. The purpose of the present paper was to review gastrointestinal (GI) bleeding occurring with occlusion of the portal system (PVs) as a complication of IORT in patients surviving long term without recurrence.

Patients: From 1990 to 1999, 45 patients underwent surgical resection of the pancreas with IORT. Eleven of these patients survived >3 years without recurrence, and occlusion of PVs was recognized in five patients at follow-up examination. Three of these five patients received repeated blood transfusions for GI bleeding.

Results: One patient had BCa and two had PCa, and pancreatoduodenectomy was carried out. The delivered radiation doses of IORT were 30 Gy (two patients) and 35 Gy (one patient). The postoperative periods to initial GI bleeding were 36, 26 and 9 months, respectively. In all cases, angiography revealed occlusion of PVs and the collateral circulation. The bleeding points were esophageal varix (case 1), remnant stomach varix (case 2) and a jejunal ulcer (case 3), and blood transfusions were carried out totaling 44, 60 and 16 units, respectively. The GI bleeding disappeared spontaneously in case 1, developed sporadically in case 2 and was stopped by metallic stent insertion in PVs in case 3.

Conclusion: During long-term follow up after pancreatectomy with IORT, it is necessary to monitor patients for GI bleeding. A clinical trial on optimum doses, long-term safety and benefit of IORT is necessary.

Key words: bile duct cancer, complication, gastrointestinal bleeding, intraoperative radiation therapy, occlusion of the portal system, pancreatic cancer.

INTRODUCTION

Carcinoma of the pancreas (PCa) and the bile duct (BCa) have a poor prognosis.[1,2] The only therapy providing a possibility of cure is surgical resection. However, postoperative survival rate is low, and various kinds of adjuvant therapy have been attempted to improve the treatment outcome.[3–9] Many reports have discussed the benefit of intraoperative radiation therapy (IORT) as adjuvant therapy in PCa[5,10–14] and Bca,[15,16] but its efficacy remains controversial. Although it is reported that there are no short-term complications after IORT,[5,10–13] there are few reports on long-term safety because patient prognosis is extremely poor. In the present study we review the prevalence of gastrointestinal (GI) bleeding occurring with occlusion of the portal system as a complication of IORT in patients surviving long term without recurrence.

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METHODS

Patients

From January 1990 to December 1999, 139 patients underwent surgical resection of the pancreas at the Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan. Of these 139 patients, 41 with PCa and four with BCa underwent IORT (Table 1): a single dose of radiation ranging from 25 to 35 Gy (mean, 30.5 Gy) was delivered to the tumor bed just after resection. Eleven of the 45 patients survived >3 years without recurrence, but occlusion of the portal system was recognized in five of these 11 patients at follow up. In three of the five patients, repeated blood transfusions were carried out for GI bleeding, and the postoperative courses of these three patients are reviewed in detail.

RESULTS

One patient had carcinoma of the distal common bile duct and the other two had carcinoma of the head of the pancreas (PhCa). Pancreatoduodenectomy (PD) was carried out in all three patients and the reconstruction method of Imanaga was adopted, which entails an end-to-end gastrojejunostomy, end-to-side pancreatojejunostomy and choledochojejunostomy.[17] In one case (case 2), wedge resection of the superior mesenteric vein (SMV) was also performed. The delivered doses of IORT were 30 Gy in two patients and 35 Gy in one patient, and the postoperative periods to initial GI bleeding were 36, 26 and 9 months, respectively (Table 2).

Case 1

A 61-year-old man underwent PD with IORT for BCa. Gastrointestinal bleeding was recognized at 36 postoperative months (POM). Computed tomography (CT) at the time of initial bleeding showed an unclear SMV but contrast of the intrahepatic portal vein (PV). Increased blood flow from the remnant stomach wall to the esophagus wall was detected. Endoscopic examination (Fig. 1a) revealed esophageal varix, which was suspected of bleeding. Portography via the superior mesenteric artery (SMA) (Fig. 1b) showed occlusion of the SMV. The collateral circulation went through the elevated jejunum, and blood flowed into the intrahepatic PV around the choledochojejunostomy. The splenic vein (SV) could not be identified on portography via the splenic artery (SA) and we diagnosed that the SV blood was flowing back through the remnant stomach and esophagus walls.

Table 1 Patients with surgical resection of the pancreas

Procedure	Cases	Survivor >3 years without recurrence	GI bleeding with occlusion of the portal sysytem
Total pancreatic resection	139†	52†	3†
IORT (–)	94†	41†	0† (0)‡
PCa, PEn	20	7	0
PCy	40	26	0
BCa	16	2	0
VCa	18	6	0
IORT (+)	45†	11†	3† (5)‡
PCa	41	9	2† (4)‡
BCa	4	2	1† (1)‡

Bca, carcinoma the bile duct; Pca, carcinoma of the pancreas; GI, gastrointestinal; IORT, intraoperative radiation therapy; Pcy, cystic tumor of the pancreas; Pen, endocrine tumor of the pancreas; Vca, carcinoma of ampulla of Vater.

IORT (–), surgical resection without IORT; IORT (+), surgical resection with IORT.

†Total number of cases for procedure; ‡no. patients with occlusion of the portal system.

Table 2 Clinical features of three patients with GI bleeding

Patient no.	Sex	Age	Diagnosis	Surgical procedure/ reconstruction	PV resection	Radiation dose of IORT (Gy)	Initial bleeding (POM)
1	M	61	BCa	PD/Imanage	–	30	36
2	F	56	PhCa	PD/Imanage	Wedge resection	30	26
3	M	57	Phca	PD/Imanage	–	35	9

BCa, carcinoma of the bile duct; GI, gastrointestinal; IORT, intraoperative radiation therapy; PD, pancreatoduodenectomy; PhCa, carcinoma of the head of the pancreas; POM, postoperative months; PV, portal vein.

Case 2

A 56-year-old woman underwent PD with IORT for PhCa. Gastrointestinal bleeding was recognized at 26 POM. Computed tomography at the time of initial bleeding (Fig. 2) demonstrated occlusion of the SMV and collateral circulation. These findings were not noted at the follow-up examination and GI bleeding of unknown cause was therefore repeated. Endoscopic examination at 90 POM (Fig. 3a) revealed bleeding of remnant stomach varix. Angiography (Fig. 3b,c) showed occlusion of the SMV. The collateral circulation flowed back to the PV through the elevated jejunum, remnant stomach and SV.

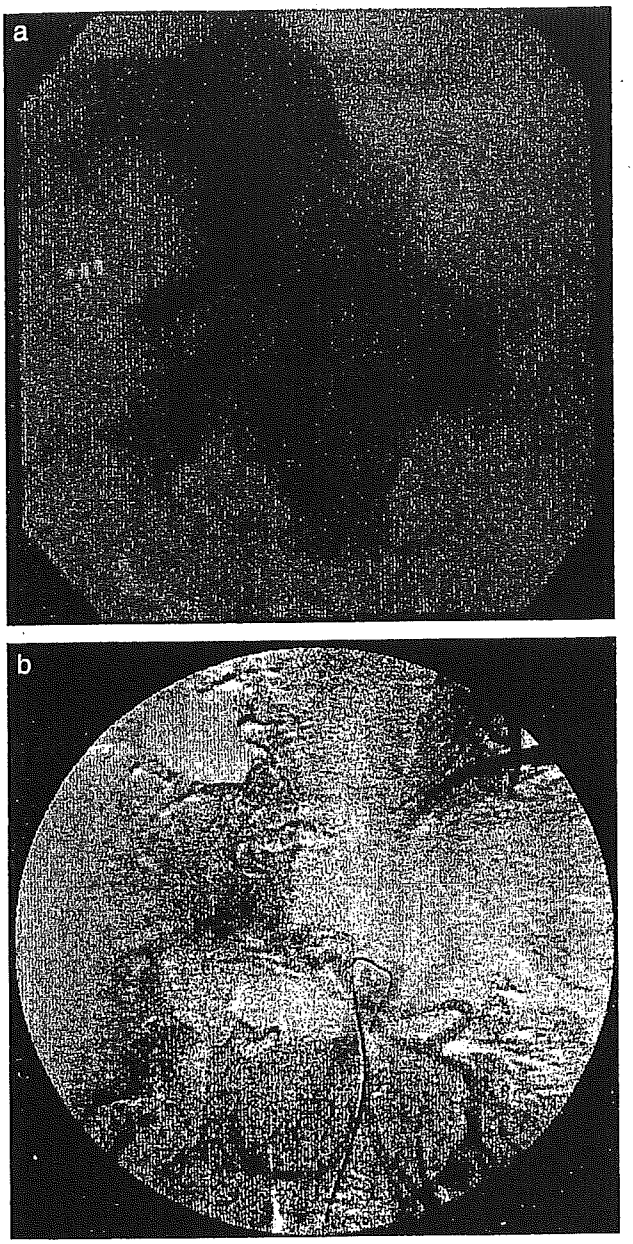

Figure 1 Case 1. Endoscopic examination revealing esophageal varix (a). Portography via the superior mesenteric artery (b) shows occlusion of superior mesenteric vein.

Case 3

A 57-year-old man underwent PD with IORT for PhCa. Gastrointestinal bleeding was recognized at 9 POM. Computed tomography at 11 POM demonstrated occlusion of the SMV and that the collateral circulation went through the elevated jejunum, anterior wall of the remnant stomach, splenic hilus and SV. Angiography (Fig. 4a) showed occlusion of the SMV, and percutaneous transhepatic portography (Fig. 4b) revealed stenosis of the SV at the portal confluence. The SV blood pressure had risen to 27 cmH_2O and PV blood pressure was 7.5 cmH_2O. Endoscopic examination at 20 POM (Fig. 4c) revealed a bleeding ulcer in the elevated jejunum.

Clinical course

Case 1 experienced repeated bleeding from 36 to 52 POM, and a total of 44 units of blood were transfused; however, there were no episodes of bleeding after 52 POM (Table 3). The patient had a relapse at 87 POM and died of cancer at 98 POM. In case 2, the first episode of GI bleeding was recognized at 26 POM and its cause was ascertained at 90 POM. During this period, a total of 60 units of blood were transfused; currently, at 98 POM, the patient is under close follow up. In case 3, the stenosis of SV at the portal confluence showed occlusion at 24 POM and a metallic stent was inserted between the PV and the SV. Gastrointestinal bleeding was not noted again until 54 POM.

DISCUSSION

In patients with PCa and BCa, the survival rate after surgical resection remains very low.[1,2] Intraoperative radiation therapy is a common adjuvant therapy to improve the treatment outcome, but its efficacy remains

Table 3 Patient clinical course

	GI bleeding (POM)	Blood transfusion (total units)	Clinical course	Recurrence	Follow-up months
1.	36–52	44	52 POM: GI bleeding (–)	+, 87 POM	98, DOD
2.	26–92	60	92 POM: close follow up	–	98, AW
3.	9–23	16	24 POM: GI bleeding (–)	–	54, AW

AW, alive and well; DOD, died of disease; GI, gastrointestinal; POM, postoperative months.

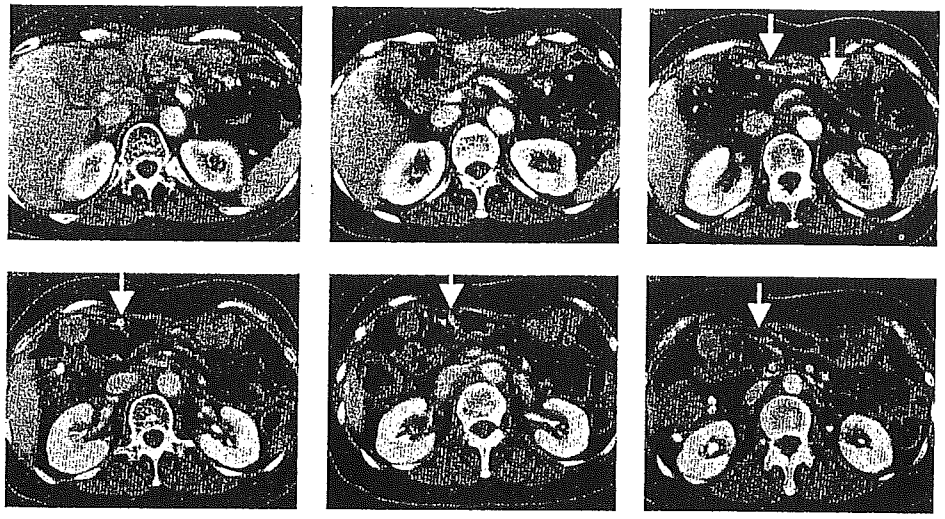

Figure 2 Case 2. Computed tomography showing occlusion of superior mesenteric vein and collateral circulation (arrows).

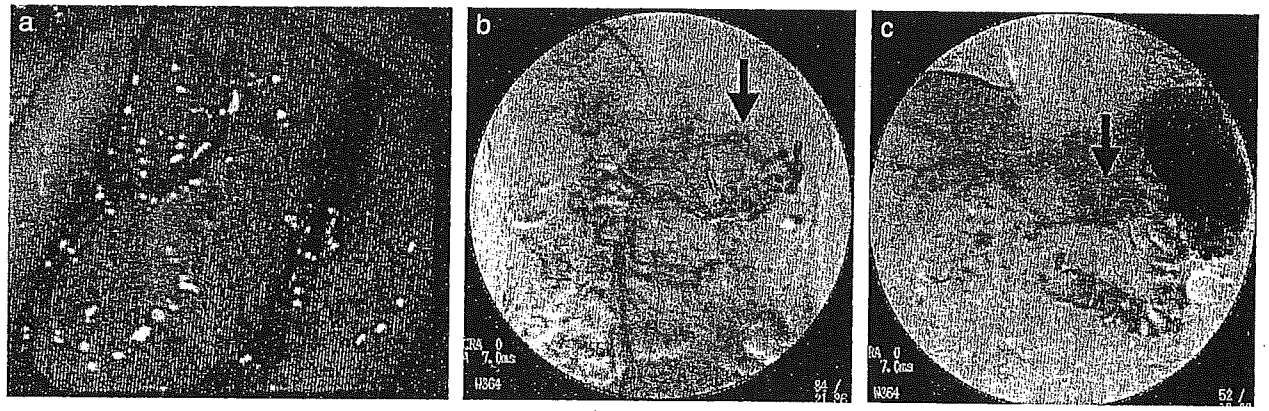

Figure 3 Case 2. Endoscopic examination demonstrating remnant stomach varix (a). Portography via superior mesenteric artery (b) and splenic artery (c) reveals occlusion of superior mesenteric vein and collateral circulation through splenic vein (arrow).

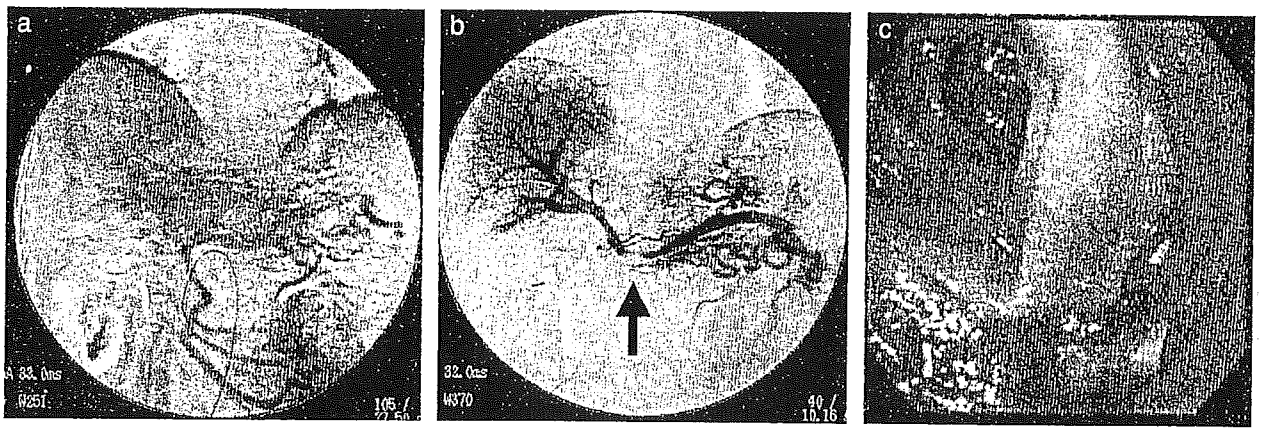

Figure 4 Case 3. Portography via superior mesenteric artery (a) and percutaneous transhepatic portography (b) at 14 post-operative months (POM) shows occlusion of superior mesenteric vein and stenosis of splenic vein (arrow). Endoscopic examination at 20 POM (c), reveals ulcer in the elevated jejunum.

controversial. While there have been reports of reduced local disease recurrence[10,11,13] and improved disease-free survival and survival rates,[12–15] it has also been reported that IORT does not extend survival time.[5,18]

Various series of trials were conducted in order to examine the benefits of IORT for PCa.[5,11–13] In all series, IORT was considered to have been safe in the short term following surgery.[5,11–13] However, because

treatment outcome of PCa is extremely poor, there are no reports of long-term safety following IORT. Autopsy analyses assessing radiation damage to various tissues after IORT have demonstrated fibrosis of the retroperitoneal soft tissues and the portal vein.[19,20] Fibrosis of tissues and occlusion of vessels in the radiation field are predicted late complications of IORT,[18] and one of the common clinical problems is GI bleeding caused by portal hypertension occurring with stenosis and/or occlusion of the portal system. Thus, in the present study we reviewed the prevalence of GI bleeding as a possible complication of IORT in patients who have survived for >3 postoperative years without disease recurrence.

Of our 11 patients who survived for >3 years without recurrence following resection of the pancreas and IORT, three (27.3%) of the five patients with subsequent occlusion of the portal system required repeated blood transfusions for GI bleeding. Unfortunately we were not able to determine whether the occlusion resulted from the operation or the influence of IORT. During the period of January 1990–December 1999, 41 of our 94 patients who underwent surgical resection of the pancreas without IORT were observed to survive for >3 years without recurrence (Table 1). Because CT is not always performed in patients with benign diseases, the precise frequency of portal occlusion in these 41 patients remains unknown. However, no occlusion of the portal system was observed in the follow-up period for these 41 patients and there were also no episodes of GI bleeding. Because lymph node dissection and nerve plexus excision were not always performed in these 41 patients, the influence of surgery on the development of portal occlusion cannot be compared simply between patients' with and without IORT. However, taken together, our findings suggest that occlusion of the PV and GI bleeding occurred as a late complication of IORT.

Intraoperative radiation therapy at lower doses (up to 20 Gy) with or without fractionated external beam radiotherapy (up to total 60 Gy) has been reported to be safe, and there was no GI bleeding as a short-term complication.[5,11,12] While Reni *et al.* reported that GI bleeding was observed in five patients (6%), the doses of IORT ranged from 10 to 25 Gy (mean 17.5 Gy) in their series.[13] In the present series patients were treated with considerably high doses of radiation ranging from 25 to 35 Gy (mean 30.5 Gy), so the risk of this complication may have been raised.

In the clinical course of case 3, a metallic stent was inserted between the PV and the SV, causing SV blood pressure to fall dramatically. Gastrointestinal bleeding was not seen again until 54 POM. There have been no reports of stent insertion for GI bleeding caused by stenosis and/or occlusion of the portal system, but this treatment is thought to be remarkably effective.

Because GI bleeding occurred with occlusion of the portal system in three of the present patients, influence of the operation itself and high-dose radiotherapy on the development of this late complication cannot be excluded. We recommend that GI bleeding is considered by physicians during the long-term follow up of patients who undergo pancreatectomy with IORT. A clinical trial on optimum doses, long-term safety and benefit of IORT is necessary.

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ORIGINAL ARTICLE

Differential diagnosis of pancreatic cancer and focal pancreatitis by using EUS-guided FNA

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Background: Despite advances in diagnostic imaging techniques, the differentiation between pancreatic cancer and focal pancreatitis remains difficult. This study evaluated the effectiveness of EUS-guided FNA in the differential diagnosis between pancreatic cancer and focal pancreatitis, with particular reference to detection of the K-*ras* point mutation.

Methods: The study included 62 consecutive patients with pancreatic ductal cancer and 15 patients with focal pancreatitis demonstrated as a pancreatic mass lesion by EUS.

Results: Sensitivity, specificity, overall accuracy, positive predictive value, and negative predictive value of cytopathologic diagnosis were 82%, 100%, 86%, 100%, and 58%, respectively. Sensitivity, specificity, overall accuracy, positive predictive value, and negative predictive value of histopathologic diagnosis were 44%, 100%, 55%, 100%, and 32%, respectively. The K-*ras* point mutation was found in 74% of pancreatic cancers and 0% of focal pancreatitis lesions. No complication of EUS-guided FNA was observed.

Conclusions: EUS-guided FNA is useful for the differential diagnosis of pancreatic mass lesions caused by pancreatic cancer and focal pancreatitis. Analysis for the K-*ras* point mutation in specimens obtained by EUS-guided FNA may enhance diagnostic accuracy in indeterminate cases. (Gastrointest Endosc 2005;61:76-9.)

Despite advances in diagnostic imaging techniques, the differentiation of pancreatic cancer from focal pancreatitis remains problematic.[1-4] Indeed, there are cases in which focal pancreatitis was misdiagnosed as pancreatic cancer or when surgery was performed because pancreatic cancer could not be absolutely ruled out. EUS-guided FNA (EUS-FNA) has been used for the differential diagnosis of pancreatic masses, staging of pancreatic cancer, and histopathologic confirmation of the diagnosis of pancreatic cancer before radiotherapy and/or chemotherapy.[5-9] However, there are few studies of K-*ras* point mutation analysis for pancreatic tissue obtained by EUS-FNA.[5,6] The present study examined the effectiveness of EUS-FNA, specifically, cytopathologic and histopathologic evaluation, and analysis of K-*ras* point mutation, for specimens obtained by EUS-FNA in the differential diagnosis of pancreatic cancer vs. focal pancreatitis.

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PATIENTS AND METHODS

The study included 62 patients with a diagnosis of pancreatic ductal cancer and 15 patients with focal pancreatitis (total 77 patients) who underwent EUS-FNA between August 1998 and April 2003 for whom the results of cytopathologic and histopathologic evaluation, and K-*ras* point mutation analysis could be obtained. Final diagnoses were confirmed by evaluation of surgical resection specimens in 8 patients (pancreatic cancer 6, focal pancreatitis 2) and by clinical follow-up of 9 months or longer for the remainder of the patients (pancreatic cancer 56, focal pancreatitis 13).

EUS-FNA was performed as previously described,[1,5,8] by using a 7.5 MHz, convex linear-array echoendoscope (GF-UCT240; Olympus Optical Co., Ltd., Tokyo, Japan) and a 22-gauge needle (NA-10J-1 or NA-11J-KB; Olympus). Aspirated material was divided into 3 parts: one for cytopathologic evaluation, another for histopathologic assessment, and the last for K-*ras* point mutation analysis.

For all 77 patients, aspirated material was immediately evaluated by a cytopathologist or a cytotechnician for rapid cytopathologic diagnosis.[5,8] Aspirated material was

TABLE 1. Clinical characteristics of patients undergoing EUS-FNA

	Pancreatic cancer	Focal pancreatitis
No. patients (M/F)	62 (40/22)	15 (10/5)
Mean age y (range)	60 (35-79)	60 (50-71)
Mean number of needle passes (range)	2.3 (1-4)	2.4 (1-4)
Location (% head)	84%	85%
Mean size of mass, mm (range)	36 (16-80)	31 (21-40)

TABLE 2. Diagnostic accuracy for cytopathologic evaluation of specimens obtained by EUS-FNA

	Pancreatic cancer	Focal pancreatitis
No malignancy	4 (7%)	15 (100%)
Suspicion of malignancy	7 (11%)	0
Malignancy	51 (82%)	0
Total	62	15

later stained by using Papanicolaou's method. For histopathologic diagnosis, material aspirated with a 22-gauge needle was directly fixed in formalin in a specimen bottle and then was embedded in paraffin. Sections then were stained (H&E). The existence of a point mutation at codon 12 in the K-*ras* gene was examined in all 77 cases by incubating the collected specimen in 10 mL of saline solution at 4°C and then by analyzing the mixture by polymerase chain reaction–single-strand conformation polymorphism (PCR-SSCP) and direct sequencing.[10-14]

Informed consent was obtained from all patients. The study was approved by the institutional review board of our hospital.

RESULTS

There was no significant difference between the patient groups with respect to age, gender, number of needle passes, and location or size of the mass (Table 1).

Cytopathologic diagnosis

Of the 62 cases of pancreatic cancer, cytopathologic assessment of the aspirated material diagnosed 4 as non-malignant, 7 as suspicious for malignancy, and 51 as malignant (Table 2). The sensitivity was 82% (51/62: 95% confidence interval [CI][73%, 92%]). Of the 15 cases of focal pancreatitis, all were diagnosed as non-malignant

Capsule Summary

What is already known on this topic

- It is difficult to differentiate between pancreatic cancer and focal pancreatitis.
- EUS-guided FNA biopsy (EUS-FNA) is very useful in the differential diagnosis of pancreatic lesions and in the diagnosis and staging of pancreatic cancer.

What this study adds to our knowledge

- K-*ras* point mutation is not seen in focal pancreatitis.
- Testing specimens obtained by EUS-FNAB for K-*ras* mutation by PCR improves the sensitivity for the diagnosis of pancreatic cancer by about 10%.

TABLE 3. Diagnostic accuracy for histopathologic evaluation of specimens obtained by EUS-FNA

	Pancreatic cancer	Focal pancreatitis
Insufficient material	7 (11%)	1 (7%)
No malignancy	11 (18%)	14 (93%)
Atypical epithelium	5 (8%)	0
Suspicious of malignancy	15 (24%)	0
Malignancy	24 (39%)	0
Total	62	15

(Table 2). The specificity was 100% (15/15: 95% CI[78%, 100%]). There was no false-positive diagnosis. The overall accuracy, positive predictive value (PPV), and negative predictive value (NPV) were 86%: 95% CI[78%, 94%]), 100%, and 58%, respectively.

Histopathologic diagnosis

The aspirated specimen was insufficient for histopathologic diagnosis in 7 of the 62 cases of pancreatic cancer: these cases were excluded from the calculations for sensitivity, specificity, overall accuracy, PPV, and NPV. Of the remaining 55 cases of pancreatic cancer, no findings indicative of malignancy were detected in 11, atypical epithelium was noted in 5, findings that raised a suspicion of cancer were present in 15, and malignancy was diagnosed in 24 cases (Table 3). The sensitivity was 44% (24/55: 95% CI[31%, 57%]) (Table 3). The aspirated specimen was insufficient for histopathologic assessment in one of the 15 cases of focal pancreatitis. No evidence of malignancy was noted in the remaining 14 cases (Table 3). The specificity was 100% (14/14: 95% CI[78%, 100%]). The overall accuracy, PPV, and NPV were 55% (38/69: 95% CI[43%, 67%]), 100%, and 32%, respectively.

TABLE 4. Detection of K-*ras* point mutation in specimens from pancreatic mass lesions obtained by EUS-FNA

K-*ras* point mutation	Pancreatic cancer	Focal pancreatitis
Positive	46 (74%)	0
Negative	16 (26%)	15 (100%)
Total	62	15

TABLE 5. Relationship between cytopathologic evaluation and K-*ras* point mutation in specimens of pancreatic cancer obtained by EUS-FNA

	Cytology	K-*ras* point mutation positive
No malignancy	4	2 (50%)
Suspicion of malignancy	7	5 (71%)
Malignancy	51	39 (76%)
Total	62	46

Detection of K-*ras* codon 12-point mutation

A point mutation was detected in 74% (46/62: 95% CI[62%, 85%]) of the 62 cases of pancreatic cancer (Table 4). Of the 46 cases in which the K-*ras* point mutation was detected, the mutation was at GAT in 22 (35.4%), at GTT in 14 (22.5%), at CGT in 9 (14.5%), and at TGT in one case (0.2%). No mutation was found in the remaining 16 cases (25.8%) of pancreatic cancer. However, no K-*ras* point mutation was observed in any of the 15 cases of focal pancreatitis. When cases with a positive K-*ras* mutation were assumed to be malignant and those negative for the K-*ras* mutation were assumed to be benign, the diagnostic accuracy was 79% (61/77: 95% CI[69%, 88%]).

Relationship between histopathologic and cytopathologic evaluation, and detection of K-*ras* codon 12-point mutation in pancreatic cancer

With respect to cytopathologic diagnosis, the K-*ras* point mutation was found in 50% (2/4) of cases, with a result of no malignancy; in 71% (5/7) of cases in which malignancy was suspected; and in 76% (39/51) of cases in which malignancy was diagnosed (Table 5). With respect to histopathologic diagnosis, the K-*ras* point mutation was detected in 43% (3/7) of cases with a result of insufficient material, in 64% (7/11) of those with no malignancy, in 80% (4/5) of cases with a finding of atypia, in 80% (12/15) of cases in which malignancy was suspected, and in 83% (20/24) of cases in which malignancy was diagnosed (Table 6).

If it is assumed that at least one positive diagnosis of cancer (cytopathologic and/or histopathologic and/or detection of K-*ras* codon 12-point mutation) was accurate, the sensitivity of EUS-FNA improved to 94% (58/62) (Table 7).

TABLE 6. Relationship between histopathologic evaluation and K-*ras* point mutation in specimens of pancreatic cancer obtained by EUS-FNA

	Histology	K-*ras* point mutation positive
Insufficient material	7	3 (43%)
No malignancy	11	7 (64%)
Atypical	5	4 (80%)
Suspicion of malignancy	15	12 (80%)
Malignancy material	24	20 (83%)
Total	62	46

TABLE 7. Sensitivity for pancreatic cancer for combined cytopathologic evaluation, histopathologic evaluation, and K-*ras* point mutation

	Pancreatic cancer
Cytology positive	51 (82%)
Cytology positive and/or histology positive	52 (84%)
Cytology positive and/or histology positive and/or K-*ras* mutation positive	58 (94%)
Total	62

Complications

No complication associated with EUS-FNA was observed in any of the 77 patients.

DISCUSSION

Compared with the rest of the GI tract, a nonoperative biopsy specimen of the pancreas is difficult to obtain. Nevertheless, there have been many studies of methods for obtaining a histopathologic or a cytopathologic diagnosis, including US- and CT-guided percutaneous biopsy, transpapillary pancreatic duct biopsy, and cytologic evaluation of pancreatic juice obtained at ERCP.[1,5,15] With the development of EUS-FNA, however, the ability to accurately diagnose pancreatic malignancy has greatly improved.[1,5,15] The ability to visualize small lesions with EUS is excellent, and, unlike other methods, the entire pancreas is readily imaged.[1,15,16] Thus, EUS-FNA is considered to be the best of the available methods for obtaining tissue samples from the pancreas. In studies that include a relatively large number of patients, the sensitivity,