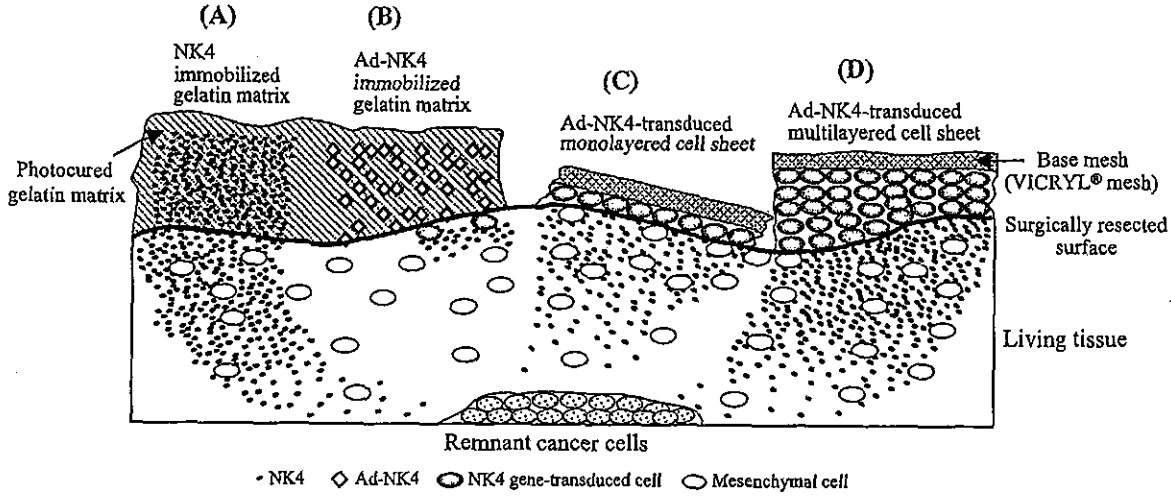

Fig. 10. Schematic of local protein delivery methods under development. (A) NK4-immobilized photocured gelatinous matrix. (B) Ad-NK4-immobilized photocured gelatinous matrix. (C) Ad-NK4-transduced monolayered cell sheet. (D) Ad-NK4-transduced multilayered cell sheet.

that the gene-transduced cell were found to be limited to on and just beneath the tissue surface. Therefore, it is highly anticipated that passive trans-tissue permeation of adenovirus, which is a giant macromolecules as compared with proteins, appears not to be effective for gene delivery [47,48]. Fig. 10 illustrates schematics of NK4- and Ad-NK4-immobilized gel layers and trans-tissue transport of NK4.

2.3. Gemcitabine (GEM) [22]

The in vitro release profile of GEM (MW; 299 g/mol) from a GEM-loaded ST-gelatin gel was characterized by an initial burst and subsequent gradual release over a prolonged period, similar to that of r-Alb from the gel. In an in vivo model using subcutaneous tumor-bearing athymic mice, rhodamine B (MW; 479 g/mol, used as a model drug of GEM) released from the ST-gelatin gel remained in the tumor at least for 10 days after photogelation on the inoculated tumor. When a GEM-loaded ST-gelatin was formed by injection, followed by subsequent photopolymerization on the inoculated tumor, the growth of the tumor was significantly suppressed without obvious adverse effects, as compared with simple GEM injection (Fig. 9B). Such suppression of tumor growth correlated with decreased cell proliferation and increased cell apoptosis in tumor cells, supported by PCNA (for proliferating cells) and TUNEL (for apoptosed cells) staining. Therefore, this strategy is considered to be highly prospective. A possible disadvantage of this system is difficulty of realization of appropriate drug-releasing profile: an adverse effect resulting from an "overdose", weak therapeutic effect due to too low dose and short releasing period due to no recharging function.

3. System II: antibody-fixed gelatinous gel (cytokine barrier) [23]

A styrene-derivatized antibody (ST-Ab), prepared with minimal affinity loss, was photocopolymerized with ST-gelatin to produce a tissue-adhesive, in situ-formed co-gel of ST-gelatin and ST-Ab, which is designed to act as a cytokine scavenger, neutralizer or barrier. A double-chamber invasion assay using an anti-HGF antibody showed that the co-gel prevented the HGF-dependent invasion of pancreatic cancer cells. On the basis of such an experimental result, when a co-gel of ST-gelatin and anti-cytokine ST-Ab is produced on a target tissue, it is anticipated that it would work well as a cytokine barrier to prevent the permeation of cytokines into the target tissue (Fig. 11A and C). Such a cytokine barrier based on an anti-cytokine fixed gel might not affect distant sites, because the antibodies were fixed in the gel, resulting in little release of the antibodies. On the other hand,

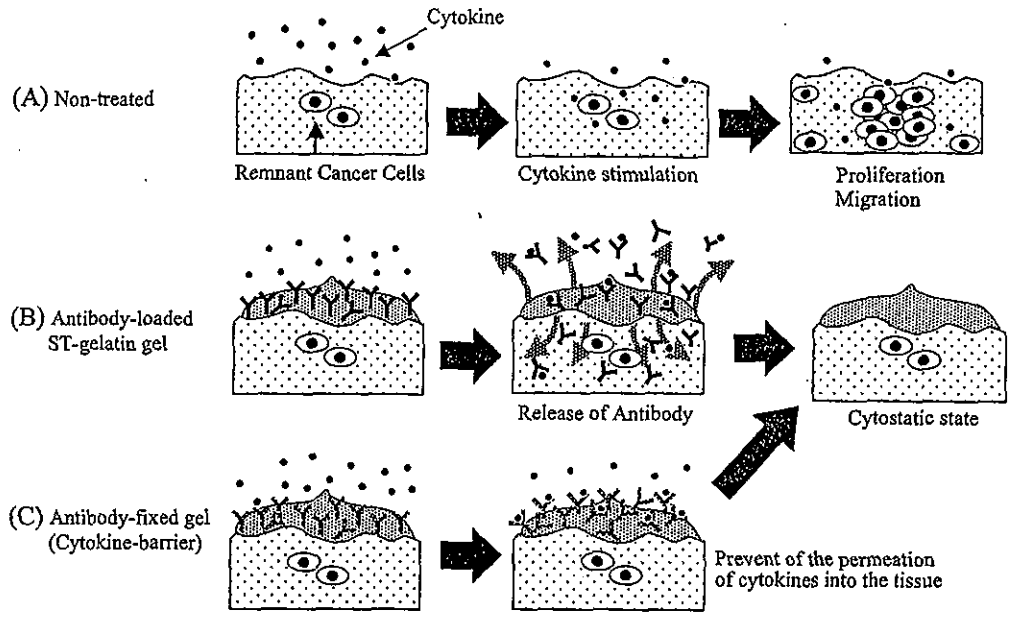

Fig. 11. Schematic of the strategy of a cytokine barrier (System II). (A) Various cytokines, produced in the intraperitoneal space during wound healing after abdominal surgery, affect remnant cancer cells in surgically resected tissues. (B) Antibody-loaded ST-gelatin gel on resected tissues. Antibodies are released from the gel, neutralize cytokines in and out of a gel, and prevent the effect of cytokines on remnant cancer cells. (C) The co-gel prepared by copolymerization of ST-gelatin and anti-cytokine ST-antibody on resected tissues. Antibodies fixed in a gel neutralize cytokines, which permeated into a gel, thereby preventing the permeation and penetration of cytokines into resected tissues [23].

when an antibody-mixed ST-gelatin solution was photogelled on a target tissue, antibodies were released from the gel and neutralized the cytokines as described above. The prevention of the permeation of cytokine into the tissue apparently results in a cytostatic state (Fig. 11). The co-gel could also be used as a drug-release matrix, from which GEM, NK4, or cytokine antibody could be released.

4. System III: cell-based delivery [24]

A hybrid tissue composed of ex vivo *NK4* gene-transduced cells was prepared for the in situ production of NK4 on a target tissue (Figs. 10C and 12). The cell source used was oral mucosal epithelial cells (OMECs), which were found to be suited to NK4 delivery because they do not secrete HGF and are easy to harvest from patients, and have reasonably high proliferation potential. OMECs were seeded on a collagen mesh-overlayered, biodegradable VICRYL® mesh, and subsequently transduced using Ad-NK4 to produce the hybrid tissue composed of NK4 gene-transduced OMECs (OMEC sheet, Fig. 12). Heterotopically implanted gene-transduced OMECs remained for at least 10 days while gradually decreasing. In an in vivo model using subcutaneous tumor-bearing nude mice, NK4 gene-transduced OMEC sheets implanted on the tumor inhibited both tumor angiogenesis (Fig. 13B) and tumor growth (Fig. 13A). Thus, it is expected that this system, developed fully using combined tissue-engineering and genetic-engineering techniques, may have great potential as a protein delivery system to target tissue at the clinical situations. The shortcomings of a prototype technology, such as the low level and short period of NK4 production, may be overcome by high density seeding of gene-transduced cells, e.g., multilayering on a microporous matrix as schematically shown in Fig. 10D. It is highly envisaged that the combination of a high cell seeding and more powerful vector enabling longer term NK4 secretion, such as retrovirus vectors, overcome the shortcomings of the prototype cell-sheet device in

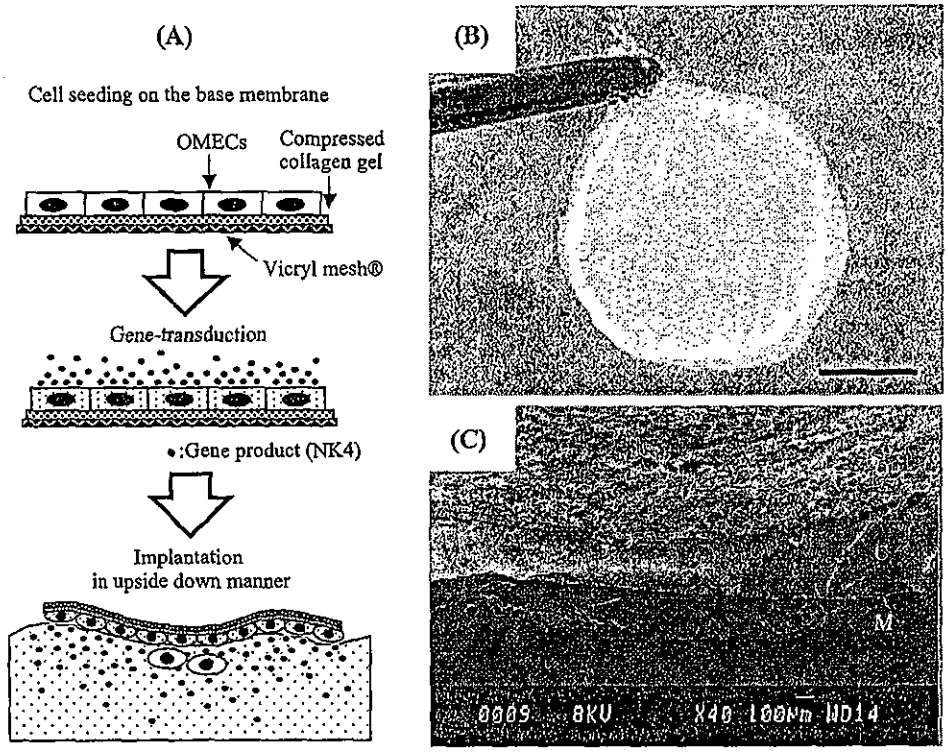

Fig. 12. System III: Cell-based delivery. (A) Schematic of gene-transduced oral mucosal epithelial cell (OMEC) sheet and the method of implantation. (B) Gross appearance of OMEC sheet. (C) Scanning electron microscopy of OMEC sheet. O, OMECs; C, collagen mesh; M, biodegradable VICRYL® mesh. Bar: 100 μm [24].

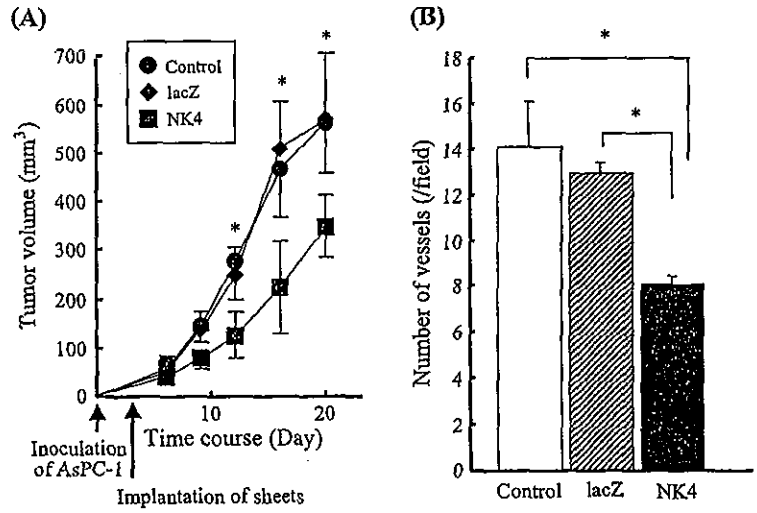

Fig. 13. Effect of NK4 gene-transduced OMEC sheet on tumor growth. Three days after cancer cell (AsPC-1) injection, tumors were covered with lacZ or NK4 gene transduced OMEC sheet. In the control group, mice were not treated. (A) Development of tumor arising from AsPC-1 cells. Values are expressed as means±S.D. (n=5, *P<0.05). (B) The number of vessels of tumors of each group. Values are expressed as means±S.D. (*P<0.05) [24].

this study. Further studies are required to increase the amount and period of in situ production of NK4.

5. System IV: device-directed delivery [25]

A rechargeable drug infusion device, which can be attached to the resected site and from which a drug is infused into the resected site, was devised (Fig. 14A). The device is composed of an elastomeric pouch (made of segmented polyurethane; SPU) having a microporous film on one side and a port connected to an elastomeric tube. The device connected to the tube guided to the extracorporeal portion permits continuous administration and recharge from the extracorporeal tube. After a few to several weeks of infusion, the device is easily removed due to the use of biodegradable sutures. The pouch is very thin (approximately 100 μm in thickness) and flexible (note that SPU, used for a diagram of artificial hearts, has proven flexibility and durability), so that the mechanically folded device is removed percutaneously through a small-sized incision upon pull-out. The prototype was fabricated with segmented polyurethane, which permits tight attachment to resected tissues using biodegradable sutures, and has multi-micropores on the side of delivery, created by a laser ablation technique coupled with computer-aided design and manufacture (Fig. 14B). In an in vivo experiment using subcutaneous tumor-bearing athymic mice, continuous infusion of GEM (150 μg/body/for 1week) from the device attached to the tumor-bearing tissue markedly suppressed tumor growth (Fig. 14C) [25]. This device, which is attached to tissue with commercially available, biodegradable sutures, can be removed easily when an adverse effect occurs or when therapy becomes unnecessary. Efforts to translate this system to the clinical situation are now underway.

6. Perspectives

The major causes of the death of patients who have undergone resection for pancreatic cancer are local recurrence and hepatic metastasis. Regarding hepatic metastasis, local chemotherapy via blood vessels has

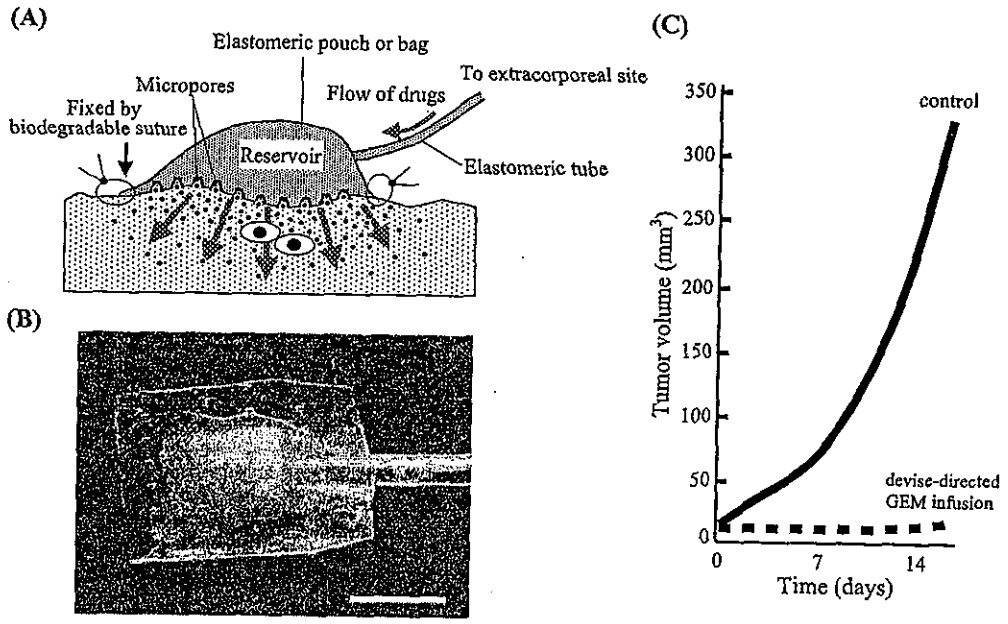

Fig. 14. System IV: Device-directed therapy. (A) Schematic of local drug delivery device. The pouch of the device is fixed on the target tissue by biodegradable sutures. Elastomeric tube connected to the pouch is guided to the extracorporeal site, which enables recharge of drugs and easy removal of the device. (B) The prototype device made by micropored segmented polyurethane. Bar: 5 mm [25]. (C) The growth of subcutaneously inoculated pancreatic cancer cell (AsPC-1). The initial tumor volume was about 20 mm^3.

been reported to reduce the occurrence of hepatic metastasis, resulting in an improvement in survival rate [40–43]. On the other hand, although several therapeutic strategies to prevent local recurrence, such as intraoperative radiotherapy, systemic chemotherapy and their combinations, have been attempted, the effect on survival rate is still under debate [9–11]. Therefore, a more effective therapeutic modality is awaited. Although a drug-delivery system used in the preclinical and clinical treatments for a variety of cancers has been reported [44–46], there have been no experimental or clinical attempts to develop a local delivery system constructed in situ on resected tissues to date. Our concept is that such a trans-tissue, local delivery system should be constructed shortly after surgical resection to minimize tumor progression caused by potent autocrine cytokines using cytostatic drugs and to enhance the cytotoxic effects of cytocidal drugs in the target tissue at very low dosage but by continuous drug exposure. For the last several years, we have been developing various new therapeutic procedures based on local drug-delivery systems as mentioned above [20–25].

Irrespective of the systems, such as a photocurable gelatinous gel (Systems I and II), a gene-transduced cell sheet (System III), and a newly devised drug-delivery device (System IV), all the therapeutic devices or materials described here can be tightly attached to the wet and uneven resected surfaces immediately after resection during surgery, and permit the local, trans-tissue delivery of various types of bioactive substances, such as anti-cancer drugs, proteins and adenoviruses, or preventing the permeation of potent tumor-progressing cytokines to the target tissue. As for the in situ gellable tissue-adhesive gel, we used photocurable gelatin which cure via visible light-induced radical polymerization of styrene group multiply derivatized on a gelatin molecule. This is originally designed to use as a hemostatic glue for surgically injured arteries during cardiovascular surgery. The rapid sol-to-gel transformation and strong tissue adhesivity withstanding against continuously loaded pulsatile stress are found to be very advantageous for trans-tissue drug delivery. Other potential candidate polymers, which meet the requirements for this particular application, may be thermoresponsible polymers which enables the sol-to-gel transformation at physiological temperature. These polymers include poly(*N*-isopropylacrylamide) or poly(ethylene glycol)–poly(propylene glycol) triblock copolymer. However, tissue adhesivity of these gels is eventually very poor due to nonionic hydrogel. In Systems I, II and IV, both cytostatic and cytocidal drugs could be delivered simultaneously, so that a more powerful synergistic effect may be expected. Caution must be paid for co-drug delivery which may cause unexpected adverse effect.

When these strategies or their combinations are applied in clinical situations as an adjuvant therapy for pancreatic cancer after thorough examination, the authors strongly envisage that the incidence of local recurrence could be reduced, hopefully resulting in a marked improvement in survival rate after surgery. To this end, research is now planned to translate these new strategic therapies in a clinical setting.

Acknowledgments

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Original Paper

Pancreatic Liver Metastases after Curative Resection Combined with Intraoperative Radiation for Pancreatic Cancer

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KEY WORDS:
Pancreatic cancer; Liver metastases

ABBREVIATIONS:
Confidence Intervals (CI); Intraoperative Radiation Therapy (IORT); Endothelial Leukocyte Adhesion Molecule-1 (ELAM-1); Deoxyribonuclease I (DNase I)

ABSTRACT

Background/Aims: A high proportion of patients even after curative resection for pancreatic cancer suffer from hepatic metastases. The aim of this study was to identify clinicopathological predictors of liver metastases after surgery, retrospectively.

Methodology: Forty-one patients underwent extended radical pancreatectomy combined with intraoperative radiotherapy, which is one of the best local control methods for ductal cell carcinoma of the pancreas. Of the 41 patients, twenty-one patients regarded as being in a cancer free state after this combined therapy were studied to analyze clinicopathological predictors of hepatic metastases. Odds ratios and their 95% confidence intervals were calculated from data using logistic regression analysis. Statistical difference was considered significant at $p<0.05$.

Results: Liver metastases after curative resection occurred in 11 patients. Preoperative biliary drainage, jaundice, elevated preoperative serum tumor-associated carbohydrate antigens levels, microscopic distal bile duct invasion, duodenal wall invasion, extrapancreatic nerve plexuses invasion were factors influencing postoperative liver metastases.

Conclusions: We found clinicopathological predictors of postoperative liver metastases. Patients with these factors require consideration in careful follow-up and perioperative adjuvant therapy for prevention of postoperative liver metastases.

INTRODUCTION

Incidence of pancreatic cancer has increased steadily in the past 60 years throughout the world (1). The prognosis is one of the most dismal of all neoplasms. Even in cases of curative resection, the outcome remains poor. Generally, the common failure patterns in treating pancreatic cancer are recurrence in the locoregional tumor bed and/or the development of hepatic metastases. We have introduced extended radical pancreatectomy combined with intraoperative radiation therapy (IORT) since 1984. This approach has provided the best control of local recurrence compared with other therapy (2). Even after this combined therapy could control local recurrence, a high proportion of patients still suffer from hepatic metastases. In the present report, clinical and histopathological data were reviewed in histological curative cases with this combined therapy retrospectively. The aim of this study was to detect predictors of postoperative liver metastases.

METHODOLOGY

Between December 1984 and December 1999, a total of 41 patients underwent extended radical pancreatectomy combined with IORT for ductal carcinoma of the pancreas at Kumamoto University. This combined therapy involves the dissection of the juxtaparaaortic and regional lymph nodes together with the connective tissue and nervous plexus around the aorta extending from the diaphragm above to the inferior mesenteric artery below. A dose of 30 Gy with 9-12 Mev electron beam radiation was administered to the operative field, following dissection as described previously (2). Of the 41 patients, twenty-seven patients underwent curative operation histologically. Six of the 27 patients were excluded from the present study, because of three patients with operative death, two with stage IVb of far advanced cancer according to Japanese classification (3), and the remaining one with another cause of death. The remaining twenty-one patients regarded as being in a cancer free state after this combined therapy were studied to analyze predictors for hepatic metastases.

No liver metastases were confirmed by intraoperative ultrasonography at surgery. Both abdominal computed tomographic scanning and ultrasonography were used to detect hepatic metastases after operation.

Factors analyzed: Clinical characteristics were analyzed including mean age, gender, and serum levels of tumor-associated carbohydrate antigens (CA 19-

Hepato-Gastroenterology 2004; 51:1500-1503

9 and/or DUPAN-2 and/or Span-1) before operation, glucose intolerance, preoperative obstructive jaundice and/or biliary infection. Within normal limits of serum CA 19-9, DUPAN-1 and Span-1 levels are 37 U/mL, 150 U/mL and 30 U/mL, respectively. All but one patient were measured for any of the serum tumor-associated carbohydrate antigens. The diagnosis of glucose intolerance was made on the basis of a fasting venous blood glucose level more than 110mg/dL, and/or glucose level more than 120mg/dL at 2 hours after uptake of 75g of glucose. Preoperative biliary drainage (endoscopic stents or percutaneous drains) was performed, because of biliary infection and/or jaundice. Obstructive jaundice was defined as serum total bilirubin level more than 1.2mg/dL with malignant biliary stenosis.

Histopathological examination of the resected specimen was studied. The resected specimens were fixed in 20% formalin solution. The paraffin sections for histological examination were prepared and stained with hematoxylin and eosin. According to Classification of pancreatic cancer defined by Japanese pancreas society (3), we evaluated histological stage, tumor size, tumor extension, extrapancreatic nerve plexuses invasion, intrapancreatic nerve invasion, lymphatic invasion, venous system invasion and lymph nodes metastases.

Statistical analysis: Odds ratios and their 95% confidence intervals (CI) were calculated from data using logistic regression analysis. Statistical difference was considered significant at $p<0.05$.

RESULTS

There were 10 women and 11 men in the study; their age ranged from 37 to 73 years, (median 57.7 years). Three patients had cancer of the pancreatic body, and 18 patients of the pancreas head. Four patients are still alive 9.5, 10.3, 156 and 190 months after operation, respectively. The cumulative survival curve in this series is depicted in **Figure 1**. The five-year survival rate was 16.0%. Of the remaining seventeen of the 21 patients, eleven patients (64.7%) suffered from hepatic metastases. Lung metastases were observed in one patient (5.9%), peritoneal dissemination in three patients (17.6%), pleural dissemination in one patient (5.9%), and remnant pancreas recurrence in one patient (5.9%) (**Table 1**).

Clinical characteristics: Clinical characteristics are shown in **Table 2**. Among these host variables, elevated preoperative serum levels of tumor-associated carbohydrate antigens ($p=0.0425$), preoperative obstructive jaundice and/or biliary infection ($p=0.0230$) were factors influencing the development of liver metastases after surgery, statistically. Ten patients (90.9%) in the group with postoperative liver metastases possessed elevated preoperative serum level of tumor-associated carbohydrate antigens, compared with three patients (44.4%) of the group without postoperative liver metastases. The median preoperative maximum total bilirubin level of all patients was 5.18mg/dL (range 0.3 to 18.2). Preoperative biliary drainage was performed because of 8 cases with jaundice and 4 cases with biliary infection. Eleven patients underwent percutaneous biliary drainage and one patient underwent endoscopic stent procedure preoperatively. Only 20.0% (2 of 10) of patients without liver metastases, compared with 90.9% (10 of 11) of patients suffering liver metastases had preoperative obstructive jaundice and/or biliary infection.

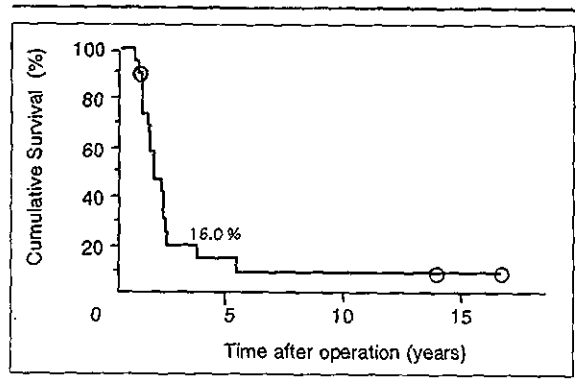

FIGURE 1 Cumulative survival rate of patients with extended radical pancreatectomy combined with intraoperative radiotherapy for ductal carcinomas of the pancreas.

Histopathological factors: Histopathological characteristics are shown in **Table 3**. With respect to histopathological factors, bile duct invasion, duodenal wall invasion and extrapancreatic nerve plexuses invasion, were significant predictive factors. Eight patients (72.7%) of the group with liver metastases had bile duct invasion, compared with only one (10.0%) of the group without liver metastases ($p=0.0075$). Seven patients (63.6%) of the group with liver metastases had duodenal wall invasion, compared with no patient of the group without liver metastases ($p=0.0128$).

TABLE 1 Mode of Recurrence in Patients with Curative Pancreatic Resection with IORT

Death caused by recurrence	17
liver metastases	11 (64.7%)
lung metastases	1
peritoneal dissemination	3
recurrence of remnant pancreas	1
pleural dissemination	1
Alive	4
Total	21

TABLE 2 Clinical Characteristics Influencing Liver Metastases

	Odds ratio	95%CI	p value
Mean age	1.04	0.95-1.1	$p=0.4535$
Gender	0.83	0.15-4.64	$p=0.835$
Tumor-associated carbohydrate antigens (+)	12.5	1.1-143.5	$p=0.0425$
Obstructive jaundice and/or biliary infection	10.7	1.4-82.0	$p=0.0230$
Glucose intolerance	6.75	0.9-49.2	$p=0.0596$

CI denotes confidence interval.

TABLE 3 Histological Characteristics Influencing Liver Metastases

	Odds ratio	95% CI	p value
Stage	5.783	0.595-56.197	$p=0.1304$
Tumor size	1.614	0.677-3-846	$p=0.2798$
Anterior pancreatic invasion	10.8	0.997-117.025	$p=0.0503$
Retroperitoneal tissue invasion	2.667	0.434-16.393	$p=0.2897$
Bile duct invasion	24.0	2.059-279.690	$p=0.0112$
Duodenal wall invasion	4.34	1.170-16.094	$p=0.0281$
Extrapancreatic nerve plexuses invasion	24.0	2.059-279.690	$p=0.0112$
Intrapancreatic nerve invasion	1.2	0.216-6.677	$p=0.8351$
Portal venous system invasion	3.375	0.290-39.332	$p=0.3316$
Lymphatic system invasion	0.245	0.039-1.523	$p=0.1312$
Venous system invasion	0.250	0.040-1.564	$p=0.1383$
Lymph nodes metastases	0.333	0.033-3.348	$p=0.3506$

CI denotes confidence interval.

Extrapancreatic nerve plexuses invasion was found in eight patients (72.7%) of the group with liver metastases, compared with only one (10.0%) of the group without liver metastases ($p=0.0075$).

DISCUSSION

Over half of the patients in this series suffered from hepatic metastases after curative operation. We found out clinical and histopathological predictors of postoperative hepatic metastases.

Preoperative jaundice and biliary drainage for cholangitis and/or jaundice are determined to be the statistically significant variables associated with postoperative hepatic metastases. We have already described enhancement effect of obstructive jaundice on development and growth of liver metastases in the rat model (4), although, its mechanism has not been unknown. Hirazawa *et al.* also reported that obstructive jaundice enhanced the growth of liver metastases due to depression of the natural killer activity of hepatic nonparenchymal cells (5). Serum level of IL-6 and tumor necrosis factor increased in experimental obstructive jaundice (6). Moreover, tumor necrosis factor is inducible endothelial leukocyte adhesion molecule-1 (ELAM-1) on endothelial cells *in vitro* (7). In the liver with cholangitis, ELAM-1 is expressed on portal tract endothelia (arterial and venous) and central vein endothelia, although weak expression of ELAM-1 on a few portal veins was found in the normal liver (7). On the other hand, elevation of preoperative serum tumor-associated carbohydrate antigen levels is also a significant variable associated with postoperative hepatic metastases in this study. Sialyl Lewis^a (CA 19-9), which is one of the tumor-associated carbohydrate antigens, plays an important role in the ELAM-1 mediated binding between human cancer cells and activated endothelial cells (8). These findings suggest that these circumstances including obstructive jaundice and cholangitis may have an advantage in formation of liver metastases of pancreatic cancer cells, which express sialyl Lewis^a.

Various changes of cell surface glycoconjugates have been found in carcinoma tissue (9). Some of these glycoconjugates are recognized as tumor-associated antigens. These include CA 19-9, DUPAN-2 and Span-1, which are frequently detected in pancreatic cancer tissues. As described before, there is a positive correlation between expression of the carbohydrate antigens and metastatic potential of pancreatic cancer not only in clinical study but also experimental study (10). Moreover, it is reported that the increased sialylation of cell surface glycoconjugates may contribute to the metastatic behavior of tumor cells (11).

Diabetic patients with pancreatic cancer tend to present with more advanced tumors, are less frequently resectable, and have a shorter survival compared to their non-diabetic counterparts (12). In addition, we have already reported that insulin enhanced invasion of pancreatic cancer cells, as a result of facilitating glucose metabolism (13). However, glucose intolerance is not associated with liver metastases after surgery in this study.

Among histopathological factors, bile duct invasion, duodenal wall invasion and extrapancreatic nerve plexuses invasion had a significant correlation with postoperative hepatic metastases. To our knowledge, our study is the first to describe histological characteristics associated with liver metastases.

No realistic therapies overcome liver metastases now. Recently, regional chemotherapy, chemoimmunotherapy and chemoradiation following pancreatic resection have been reported to be effective for improvement of survival (14-17). These strategies are supposed to be helpful to prevent liver metastases. A new strategy to use deoxyribonuclease I (DNase I) for blood-borne metastasis has been reported (18). DNase I prevents blood-borne metastasis. Combined anticancer agents with other drugs including DNase I should be considered to prevent them. We also tried to resect liver metastases from the pancreas in three cases. Two of three survived more than five years after first resection of the pancreatic cancer, even though, indication of this resection is limited to localized liver metastases and no evidence of local recurrence (19).

In conclusion, we found clinicopathological predictors of liver metastases after surgery. Patients with these factors require consideration in careful follow-up and perioperative adjuvant therapy for prevention of postoperative liver metastases.

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Case Report

Inferior Head Resection of the Pancreas and Cyst Resection for Choledochal Cyst with Chronic Calcifying Pancreatitis

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KEY WORDS:
Choledochal cyst; Anomalous arrangement of pancreaticobiliary duct; Chronic calcifying pancreatitis; Pancreatic head resection; Inferior head resection of the pancreas

SUMMARY

We report inferior head resection of the pancreas and cyst resection for congenital choledochal cyst with an anomalous arrangement of pancreaticobiliary duct and chronic calcifying pancreatitis. A 42-year-old man was admitted to the National Cancer Center Hospital East complaining of back pain. Contrast-enhanced computed tomography showed marked dilatation of the bile duct and multiple pancreatic stones in the main pancreatic duct. Endoscopic retrograde cholangiopancreatography demonstrated pancreatic stones in the dilated main pancreatic duct. The patient underwent cyst excision, inferior head resection of the pancreas, hepaticojejunostomy and lateral pancreaticojejunostomy. The postoperative course was uneventful. This procedure relieved the back pain. Choledochal cyst with anomalous arrangement of the pancreaticobiliary duct is frequently associated with acute pancreatitis. Inferior head resection of the pancreas removed the common channel which could be the cause of relapsing pancreatitis. Thus, inferior head resection can play a role in the management of choledochal cyst with chronic pancreatitis.

INTRODUCTION

Choledochal cyst with an anomalous arrangement of pancreaticobiliary duct is sometimes associated with acute pancreatitis (1-4). However, the association between choledochal cyst and chronic pancreatitis is not fully understood. We report a case of congenital choledochal cyst with anomalous arrangement of pancreaticobiliary duct and chronic calcifying pancreatitis treated by resection of the choledochal cyst, common channel, and inferior pancreatic head (5).

CASE REPORT

A 42-year-old man was admitted to the National Cancer Center Hospital East complaining of back pain. The patient did not have a history of alcohol abuse. On admission, physical examination revealed that his abdomen was soft with no palpable masses. Laboratory data showed elevated serum γ-GTP level (534 IU/L, normal range: 12-73 IU/L) and serum leucine aminopeptidase level (105 IU/L, normal range: 30-70 IU/L). Serum amylase level (41 IU/L) was normal. Contrast-enhanced computed tomography showed marked dilatation of the bile duct and multiple pancreatic stones in the main pancreatic duct (**Figure 1**). Endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography demonstrated dilatation of the common bile duct (38mm in diameter) and stones in the dilated main pancreatic duct and common channel (**Figures 2 and 3**). On the basis of these findings, we made the diagnosis of choledochal cyst with anomalous arrangement of pancreaticobiliary duct and chronic calcifying pancreatitis. At laparotomy, intraoperative ultrasonography showed multiple stones in the dilated main pancreatic duct. The patient underwent cyst excision, inferior head resection of the pancreas (5), hepaticojejunostomy and lateral pancreaticojejunostomy. The common channel and uncinate process were removed. Reconstruction was performed by Roux-en-Y hepaticojejunostomy with lateral pancreaticojejunostomy using a free jejunal loop. The postoperative course was uneventful, and the patient was discharged from hospital on the 41st postoperative day. This procedure completely relieved the back pain. He is

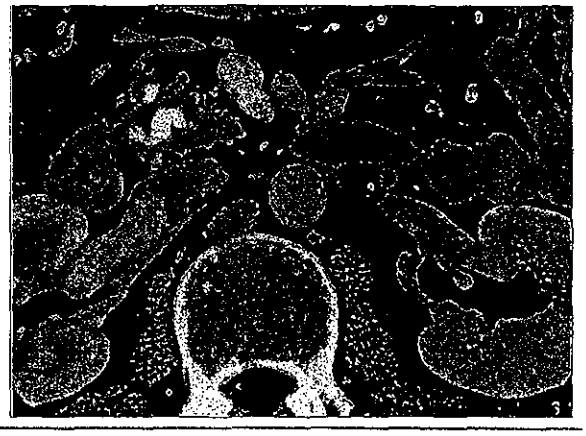

FIGURE 1
Contrast-enhanced computed tomography showed marked dilatation of the bile duct and multiple pancreatic stones in the main pancreatic duct.

Hepato-Gastroenterology 2004; 51:1504-1505

Preoperative Detection of Liver Metastases Secondary to Pancreatic Cancer

Utility of Combined Helical Computed Tomography During Arterial Portography With Biphasic Computed Tomography–Assisted Hepatic Arteriography

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Objective: This study was designed to define the diagnostic advantage of computed tomography during arterial portography combined with computed tomography–assisted hepatic arteriography (CTAP + CTHA) for preoperative detection of liver metastases secondary to pancreatic cancer compared with that of multidetector computed tomography (MDCT).

Methods: From January 2002 to February 2003, we retrospectively studied 19 consecutive patients with pancreatic cancer. MDCT was performed on all patients prior to preoperative visceral angiography. Fourteen patients underwent CTAP + CTHA at the time of preoperative angiography.

Results: Liver metastases were identified in 3 patients by means of MDCT. Of 14 patients who underwent CTAP + CTHA, 8 patients (57.1%) were diagnosed as having liver metastases, which could not be detected by MDCT. These tumors missed by MDCT ranged from 5 to 15 mm in size. On CTAP + CTHA, a single nodule in the liver was detected in 2 patients, 2 nodules in 2 patients, 3 lesions in 1 patient, and ≥4 lesions in 3 patients. The sensitivity and specificity of CTAP + CTHA versus MDCT were 75.0% versus 23.1% and 66.7% versus 100%, respectively.

Conclusions: In conclusion, the combination of CTAP and CTHA is useful to confirm liver metastases before operation for resectable pancreatic cancer because it has higher sensitivity to detect of liver metastases compared with MDCT.

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Key Words: liver metastases, pancreatic cancer, computed tomography during arterial portography, computed tomography–assisted hepatic arteriography

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The prognosis of pancreatic adenocarcinoma still remains dismal, with a 5-year survival rate of 4%.[1] Despite improvements in imaging technology, <20% will be potentially resectable at the time of initial diagnosis.[1] Complete pancreatic resection can yield actuarial 5-year survival rates of 15%–25% following pancreaticoduodenectomy[2–4] and 8%–14% following distal pancreatectomy.[5,6] Surgery is the only curative treatment, but even after curative resection of pancreatic carcinoma, most patients have a recurrence including approximately 62% of liver metastases.[7,8] A high recurrence rate of liver metastases in the early period after surgery might implicate that liver metastases are present at the time of operation but below the threshold (microscopic) of detection by current preoperative radiologic imaging and intraoperative examination. Therefore, more precise evaluation for hepatic lesions is necessary because accurate detection of liver metastases has major implications in guiding both appropriate treatment and defining prognosis.

This study was designed to evaluate the diagnostic advantage of computed tomography during arterial portography combined with computed tomography–assisted hepatic arteriography (CATP + CTHA) for preoperative detection of liver metastases secondary to pancreatic cancer compared with that of multidetector computed tomography (MDCT).

PATIENTS AND METHODS

We retrospectively studied 19 consecutive patients with pancreatic cancer from January 2002 to February 2003.

All CT scans were obtained with a MDCT (Lightspeed QXi; General Electric Medical System, Milwaukee, WI). Im-

aging parameters were established as a pitch of 3 with a table speed of 15.0 mm/rotation to visualize the arterial phase and portal venous phase. All phases were acquired in a cranial-to-caudal direction. An 18- or 20-gauge intravenous catheter was placed in the patients' antecubital vein. A total of 100–120 mL iopamidol 300 (Iopamiron; Nihon Schering, Osaka) was infused using a power injector at a rate from 3–4 mL/s. Thirty seconds after the start of infusion, entire liver imaging was performed during a breath-hold. Subsequently, the portal venous phase was obtained following 70 seconds of scan delay. Each image was reconstructed with contiguous 5-mm slice thickness.

CTAP + CTHA was performed at the time of preoperative angiography after no remote metastasis was confirmed on CT. All studies were performed with an IVR-CT system (Toshiba Medical Systems), which comprised a digital subtraction angiography system (KXO-80C/DFP-2000A; Toshiba Medical Systems) and helical CT scanner (X-Vision; Toshiba Medical Systems). This equipment is capable of performing digital subtraction angiography and CT scanning with the patients in one position. A 5-French catheter was inserted via the right femoral artery with Seldinger technique, followed by positioning the tip of the catheter in the superior mesenteric artery, and testing the infusion capacity of the vessel. Subsequently, helical CT during the injection of the contrast medium into the superior mesenteric artery was performed for CTAP (Figs. 1A and 2A). CTAP was performed using 90 mL of contrast material (Optiray 160; Tyco Japan, Tokyo, Japan) injected at a rate of 2.5 mL/s. The CT scanning was performed 25 seconds after the start of the injection.

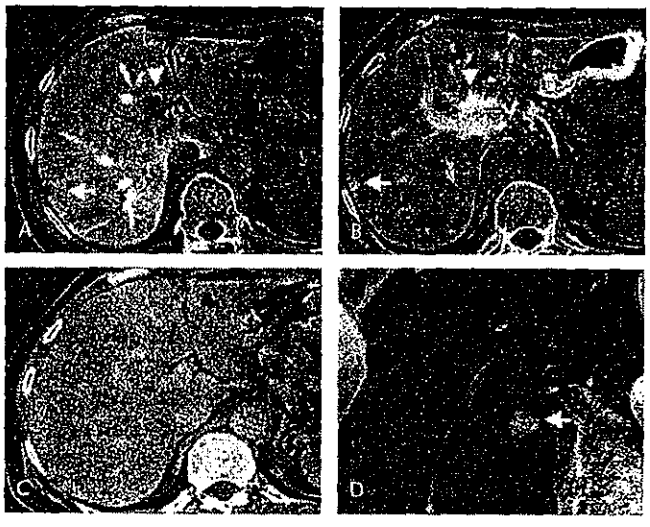

FIGURE 1. A 61-year-old woman with 2 liver metastases from cancer of the head of the pancreas. A, CTAP shows the tumors as areas of discrete portal perfusion defects (arrows). B, CTHA revealed focal enhanced lesions (arrows). C, MDCT could not detect liver metastases. D, Operative findings showed the same lesion as detected on CTAP + CTHA (arrow).

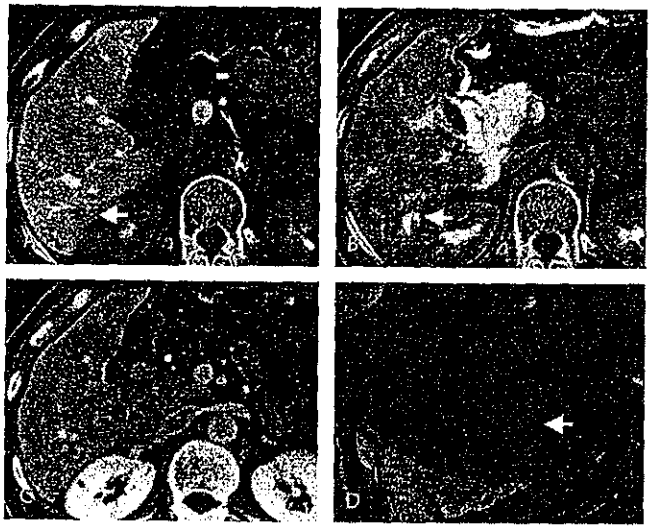

FIGURE 2. A 62-year-old man with liver metastases from cancer of the tail of the pancreas. A, A 15-mm hypoattenuated lesion is noted on the CTAP scan in segment 6 (arrow). B, CTHA shows a focal enhanced lesion, which is the same place detected by CTAP (arrow). C, MDCT could not detect liver metastases. D, Operative findings showed the same lesion as detected on CTAP + CTHA (arrow).

For CTHA, the tip of the catheter was placed in the common hepatic artery and the biphasic CT was performed during the injection of the contrast medium into this artery starting at 5 seconds after the start of the injection (Figs. 1B and 2B). CTHA was performed using 45 mL of Optiray 160 injected at a rate of 1.5 mL/s.

In all patients, MDCT and CTAP + CTHA studies were performed within 2 weeks.

All MDCT scans were reviewed by 2 experienced abdominal radiologists in consultation. At the MDCT reading, the readers knew that the patients had pancreatic carcinoma, but information about liver metastases was not given. They evaluated images of combination of plain, arterial phase, and portal venous phase images of MDCT. CTAP + CTHA images were evaluated independently just after the examination by different experienced radiologists in consultation. Lesions, which were hypoattenuated on CTAP and enhanced on CTHA, were diagnosed as liver metastases. The presence of each lesion at diagnosis was defined as positive histologic proof at operation or enlargement of the lesions during the follow-up period on radiologic examinations. The absence of liver metastasis at diagnosis was proved by intraoperative findings including ultrasound (US) for operative cases and/or follow-up radiologic examinations of >6 months.

RESULTS

The characteristics of the 19 patients are outlined in Table 1. There were 9 women and 10 men in this study. The average age of the patients was 61 years (range, 43–78). Of 19

TABLE 1. Patients' Characteristics

No. of patients	19
Age (y)	
Median	61
Range	43–78
Male/female	10/9
Extension of primary tumor*	
T1	1
T2	0
T3	12
T4	6
Site of primary lesion	
Head	8
Body	8
Tail	3

*According to the TNM classification.

patients, 18 were included in extrapancreatic diseases (12 in T3, 6 in T4) according to the TNM classification.[9] Pancreatic tumor was limited to the pancreas in only 1 patient. The primary lesion of the pancreas was located in the head for 8 patients, in the body for 8 patients, and in the tail for 3 patients (Table 1).

Figure 3 is a schematic diagram of diagnoses in preoperative liver metastases secondary to pancreatic cancer with MDCT and CTAP + CTHA in this study. Liver metastases were detected by MDCT in 3 patients. These lesions were characterized by multiple and huge lesions ranging from 43 to 80 mm in maximal diameter. Of the 16 patients who had no evidence of liver metastases on MDCT, 14 patients underwent CTAP + CTHA. The remaining 2 patients of the 16 underwent surgery without CTAP + CTHA being performed. These 2 patients had liver metastases that were detected by MDCT 2 and 4 months after pancreatic resection.

Of the 14 patients who underwent CTAP + CTHA, liver metastases were revealed in 8 patients (57.1%). These liver

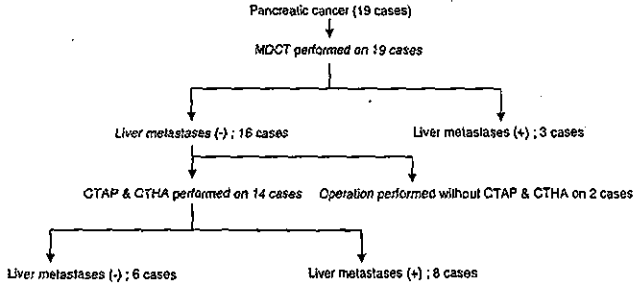

FIGURE 3. Schematic diagram of diagnoses in preoperative liver metastases secondary to pancreatic cancer by MDCT and CTAP + CTHA.

metastases missed by MDCT ranged from 5 to 15 mm in size. Most of them were within 10 mm in diameter. A single nodule in the liver was detected in 2 patients, 2 nodules in 2 patients, 3 lesions in 1 patient, and ≥4 lesions in 3 patients by CTAP + CTHA (Table 2).

Three of the 8 patients underwent pancreatectomy, and hepatic nodules were confirmed at the same site as detected by CTAP + CTHA. In 2 of the 3 cases, these lesions were resected, and proof of adenocarcinoma was obtained histologically. In case 4 in Table 2, 7- and 15-mm hypoattenuated lesions were detected in segments 6 and 4 of the liver by CTAP, respectively. These lesions were enhanced by CTHA but not detected by MDCT. A 7-mm lesion in segment 6 of the liver was extirpated and confirmed as liver metastases from pancreatic cancer histologically (Fig. 1). In case 7 in Table 2, CTAP + CTHA also revealed 2 metastatic lesions in segments 6 and 7 of the liver (15 and 10 mm in diameter), which were missed by MDCT. A 15-mm lesion in segment 6 of the liver was extirpated and confirmed as liver metastases from pancreatic cancer histologically (Fig. 2).

Table 3 summarizes the clinical courses of the 14 patients who underwent CTAP + CTHA. Liver metastases were enlarged in 4 cases; however, lesions could not be verified in the 2 cases by MDCT during the follow-up period (4–15 months). Hepatic lesions were diagnosed as adenocarcinoma in the 2 cases histologically. Therefore, of the 8 cases of liver metastases detected by CTAP + CTHA, 6 cases were diagnosed accurately. On the other hand, of the 6 cases diagnosed by CTAP + CTHA as having no liver metastases, 2 patients had liver metastases and in the other 4 patients, metastases could not be detected by MDCT during follow-up period (6–16 months). Therefore, the sensitivity and specificity of CTAP + CTHA versus MDCT were 75.0% (6 of 8) versus 23.1% (3 of 13) and 66.7% (4 of 6) versus 100% (6 of 6), respectively.

DISCUSSION

The major finding of this study is that the combination of CTAP and CTHA has sensitivity superior to that of MDCT for

TABLE 2. Characteristics of Liver Metastases Detected by CTAP + CTHA and Missed by MDCT

Case	No. of Metastases	Size of Metastases (mm)
1	Multiple	7–10
2	Multiple	5–10
3	1	10
4	2	7, 15
5	Multiple	5–10
6	1	7
7	2	10, 15
8	3	7

TABLE 3. Treatment and Clinical Outcome of Patients Who Underwent CTAP + CTHA

Case	Liver Metastases on CTAP + CTHA	Treatment	Liver Metastases During Clinical Course	Outcome (Cause of Death)
1	Detected	Chemoradiation	ND on MDCT	Alive; 10 mo
2	Detected	Chemotherapy	Enlargement on MDCT	Death; 8 mo (liver metastases)
3	Detected	Chemoradiation	Enlargement on MDCT	Death; 15 mo (liver metastases)
4	Detected	PpPD, chemotherapy	Histological confirmation	Alive; 10 mo
5	Detected	Chemoradiation	Enlargement on MDCT	Death; 17 mo (liver metastases)
6	Detected	DP, chemotherapy	Enlargement on MDCT	Death; 4 mo (liver metastases)
7	Detected	DP, chemotherapy	Histological confirmation	Alive; 12 mo
8	Detected	Chemoradiation	ND on MDCT	Death; 8 mo (dissemination)
9	ND	Chemoradiation	Detected on MDCT	Alive; 10 mo
10	ND	PpPD, chemotherapy	Detected on MDCT	Death; 14 mo (liver metastases)
11	ND	Chemoradiation	ND on MDCT	Alive; 16 mo
12	ND	Probe laparotomy chemotherapy	ND on MDCT	Death; 10 mo (dissemination)
13	ND	Bypass, chemotherapy	ND on MDCT	Death; 6 mo (dissemination)
14	ND	PpPD, chemotherapy	ND on MDCT	Alive; 16 mo

PpPD, pylorus preserving pancreaticoduodenectomy; DP, distal pancreatectomy; ND, not detected; MDCT, multidetector computed tomography.

preoperative diagnosis in liver metastases from pancreatic cancer. Over half of liver metastases, which could not detected by MDCT, could be detected by CTAP + CTHA. Sizes of these metastatic lesions were within 15 mm, and most of the lesions were within 10 mm in diameter. A certain correlation exists between the site of the primary tumor and the gross appearance of the liver metastases.[10] Liver metastases secondary to pancreatic cancer have often been detected as multiple and small lesions, especially when within 10 mm in diameter. Foroutani et al[11] reported that the sensitivity of triphasic CT scanning was 100% for the detection of hepatic tumors >3 cm in diameter, but smaller nodules tended to be missed by CT scan (28.6% of the lesions <1 cm, 15.8% of those 1–2 cm). Jimenez et al[12] reported that >40% of cases predicted to be resectable by CT were not resectable during surgical laparotomy because of small metastases of the liver and peritoneal dissemination lesions missed in most cases. From this point of view, the combination of CTAP and CTHA is well qualified for preoperative evaluation of the existence of liver metastases from pancreatic cancer.

Angiography-assisted CT can afford a very high accuracy for tumor detection when CTHA is combined with CTAP.[13] Inaba et al[14] also revealed that the diagnostic accuracy was statistically higher with CTAP + CTHA than with CTAP alone for hepatic metastases from colorectal cancer. Furukawa et al[15] reported that CTAP conferred no advantage over intravenous contrast-enhanced CT for the evaluation of liver metastases from pancreatic carcinoma. Although CTAP is a very sensitive imaging, its specificity is quite low, suggesting that CTAP + CTHA, not CTAP alone, should be used to evaluate preoperative liver metastases from pancreatic cancer.

Over the past decade, laparoscopy has emerged as a popular method for detecting extrapancreatic diseases; however, the efficacy of laparoscopy, including laparoscopic US, is still controversial.[16] It is clear that laparoscopy can prevent unnecessary exploratory laparotomy for patients who have image-occult metastatic disease manifested by laparoscopically detectable superficial liver metastases.[16] However, it is impossible to detect small nodules located deep in the liver by means of laparotomy and intraoperative palpation. CTAP + CTHA is especially valuable to detect deep small hepatic metastases.

Superparamagnetic iron oxide (SPIO)–enhanced MRI has not only improved tumor detection but also allowed characterization of liver lesions.[17] Strotzer et al[17] stated that spiral CTAP cannot be replaced by SPIO-enhanced MRI because CTAP has higher sensitivity, although its specificity is relatively low. Vogl et al[18] also reported that the diagnostic efficacy of SPIO-enhanced MRI is similar to that of CTAP. US offers the most a widespread, noninvasive, and relatively inexpensive examination for the detection of liver metastases. However, the sensitivity of US for detecting lesions <1 cm is difficult to establish.[19] We could not compare CTAP + CTHA with SPIO-MRI and US for the detection of liver metastases from pancreatic cancer in this study. However, due to the low spatial resolution of MRI, it is extremely difficult to detect small metastatic nodules on SPIO-enhanced MRI, especially when lesions are located at the edge of the liver. Yamaguchi et al[20] have also shown that CTAP was significantly better than US for detecting metastases <10 mm in diameter in a prospective evaluation of liver resection for colorectal metastases. Although no complication related to CTAP + CTHA has occurred in this study, this is actually a more invasive examina-

tion than SPIO-MRI and US. The application of CTAP + CTHA may be limited to resectable cases proved by other imaging. The diagnostic accuracy of CTAP + CTHA should be compared with that of SPIO-MRI and US in a size-by size study for liver metastases from pancreatic cancer in the future.

In conclusion, the combination of CTAP and CTHA is useful to confirm liver metastases before operation for resectable pancreatic cancer because it has higher sensitivity for the detection of liver metastases compared with MDCT.

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Case report

Metastatic gastric tumor secondary to pancreatic adenocarcinoma

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Metastatic disease, from the pancreas, involving the stomach is an unusual clinical event. Local recurrence, liver metastases, and peritoneal spread are the most common recurrent patterns after curative resection of pancreatic cancer. We report a patient who suffered from gastric metastasis secondary to pancreatic adenocarcinoma 1 year after pancreatectomy. A 49-year-old woman underwent distal pancreatectomy with intraoperative radiation therapy for cancer of the body of the pancreas in October 2002. The histological diagnosis was well-differentiated adenocarcinoma of the pancreas, stage IIB; T1N1M0. Multiple liver metastases were detected on computed tomography (CT) in March 2003. Combination chemotherapy of 5-fluorouracil hepatic arterial continuous infusion and systemic gemcitabine administration led to the disappearance of the liver metastases on CT in September 2003. One month later, she complained of epigastric pain and underwent gastric endoscopy, which revealed a submucosal tumor in the fornix posterior wall. Histological diagnosis of the biopsy specimen was well-differentiated adenocarcinoma, and immunohistochemical studies, using anti-cytokeratin 7 and -20 monoclonal antibodies, were compatible with gastric metastasis from pancreatic carcinoma. A F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) scan revealed a high-uptake lesion, which coincided with the gastric tumor. No other abnormal uptake could be found. Histopatholoical examination of the resected specimen revealed submucosal growth of the metastatic cancer (well-differentiated adenocarcinoma).

Key words: gastric metastasis, pancreatic adenocarcinoma, FDG-PET scan

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Introduction

Secondary neoplasm involvement of the stomach seems to be rare from an anatomical point of view, but the incidence of this condition was 0.2%–1.7% in several autopsy series of cancer patients.[1–4] Postmortem studies reveal higher incidences of cancer metastases than clinical studies, because clinically latent metastases, which are under the sensitivity of imaging, are discovered at autopsy. The three most common metastatic tumors of the stomach are derived from lung and breast cancers and malignant melanoma.[5] Pancreatic adenocarcinoma still has a dismal prognosis, with a 5-year survival of 4%.[6] Surgery is the only curative treatment, but even after curative resection of pancreatic carcinoma, most patients suffer from recurrence, including liver metastases, peritoneal dissemination, and local recurrence.[7,8] Metastatic disease, involving the stomach, from pancreatic cancer is an unusual clinical event. We report a case of gastric metastasis that occurred 1 year after surgery for pancreatic adenocarcinoma.

Case report

A 49-year-old woman underwent distal pancreatectomy with intraoperative radiation therapy for cancer of the body of the pancreas in October 2002. The histological diagnosis was well-differentiated adenocarcinoma of the pancreas (Fig. 1a), stage IIB; T1N1M0, according to the TNM classification.[9] In March 2003 multiple liver metastases were detected on computed tomography (CT), along with elevation of serum carbohydrate antigen (CA) 19-9 level (Fig. 2). Combination chemotherapy of 5-fluorouracil hepatic arterial continuous infusion and systemic gemcitabine administration led to disappearance of the liver metastases on CT, with normalization of the serum CA 19-9 level (Fig. 2) in September 2003. In October 2003 she complained of

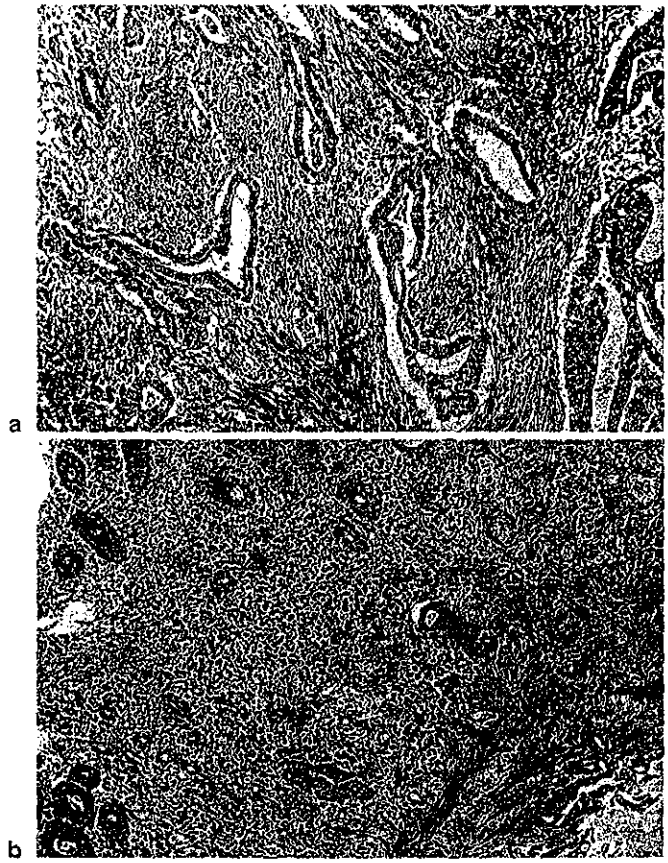

Fig. 1. **a** Histological examination of resected specimen showed well-differentiated adenocarcinoma of the pancreas. **b** Histological diagnosis of biopsy specimen of the gastric tumor was well-differentiated adenocarcinoma; the tumor was present in the submucosa, and was covered with normal mucosa. **a** *H&E*, ×100; **b** *H&E*, ×40

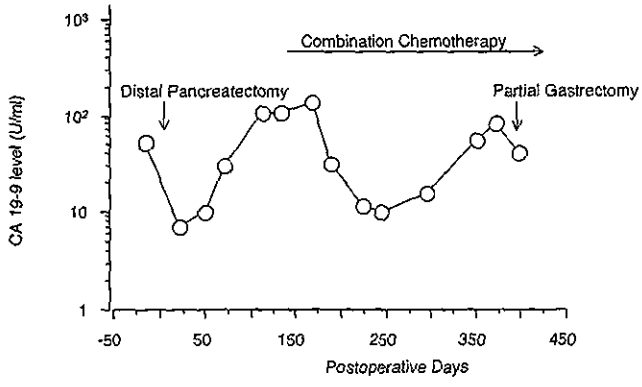

Fig. 2. Correlation of treatments with changes of serum carbohydrate antigen 19-9 (CA 19-9) levels. Levels of CA 19-9 of less than 37 U/ml are within normal limits. Postoperative days are counted after distal pancreatectomy

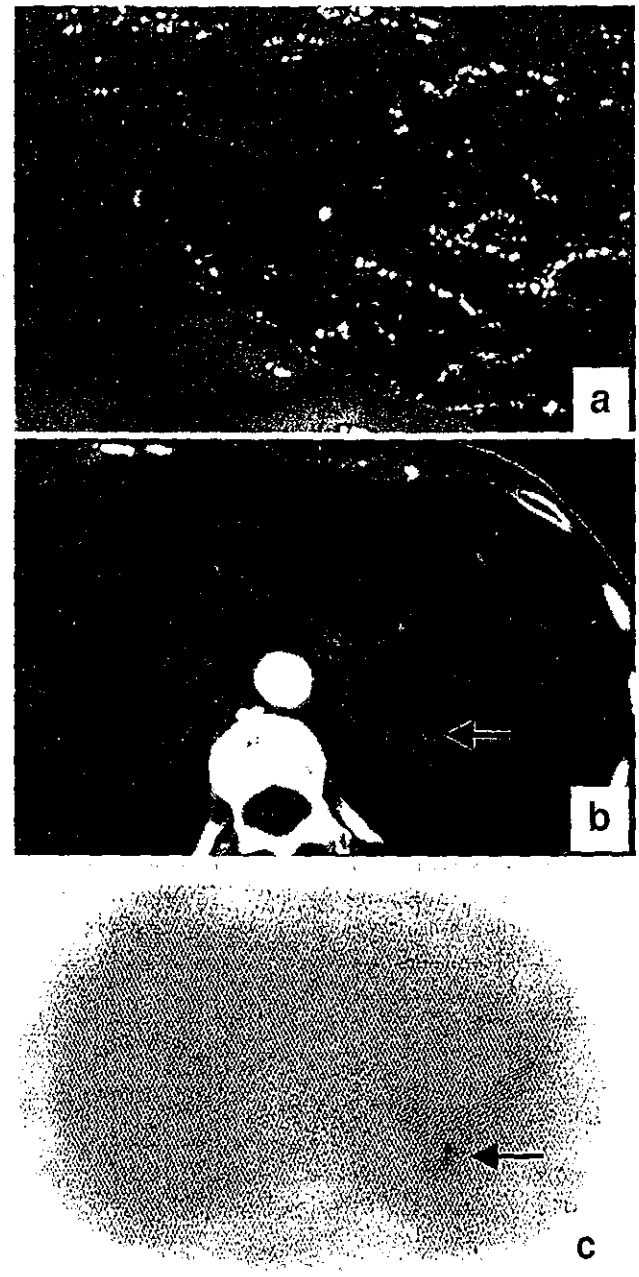

Fig. 3. **a** Gastric endoscopy showed a submucosal tumor in the fornix posterior wall. **b** Computed tomography revealed a ringed-enhanced mass lesion in the fornix posterior wall. **c** F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) scan revealed a high-uptake lesion (*arrow*), identified as a gastric tumor. No other abnormal uptake was found

epigastric pain, and underwent gastric endoscopy, which revealed a submucosal tumor in the fornix posterior wall (Fig. 3a), with elevation of the serum CA 19-9 level (Fig. 2). Histological diagnosis of the biopsy specimen of the tumor was well-differentiated adenocarcinoma (Fig. 1b). In addition, immunohistochemical studies, using anti-cytokeratin 7 and -20 monoclonal antibodies, showed positivity for cytokeratin 7 and negativity for cytokeratin for 20 in the gastric tumor. The expressions of these cytokeratin subtypes in the

Fig. 4. Histopathological examination revealed submucosal growth of metastatic cancer, which was covered with normal gastric mucosa. H&E, ×20

gastric tumor showed the same pattern as those in the resected pancreatic adenocarcinoma. A CT scan showed a ring-enhanced tumor, 15 mm in diameter, in the fornix posterior wall (Fig. 3b). A F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) scan revealed a high-uptake lesion in the fornix posterior wall; no other abnormal uptake could be found (Fig. 3c).

We performed an operation on November 19, 2003. A gastric tumor was found in the same place as the lesion detected on preoperative examinations, and no other metastatic lesion was detected in the abdomen. Partial gastrectomy was performed. Histopathological examination revealed submucosal growth of the metastatic adenocarcinoma, covered with normal gastric mucosa (Fig. 4). The serum CA 19-9 level decreased after the gastrectomy (Fig. 2). The patient's postoperative condition was good, and she was discharged home on the twentieth postoperative day.

Discussion

Gastric metastases from pancreatic adenocarcinoma are rare clinical events. These metastases were reported at autopsy studies, mainly.[2–4] Griffin et al.[7] reported that, after curative resection of pancreatic cancer, 73% of patients had local recurrence, while liver metastases were found in 62%, and peritoneal spread was documented in 42%. Therefore, in most patients with pancreatic adenocarcinoma even if metastatic gastric tumors existed, the patients might die before the detection of a gastric tumor by clinical examinations. Besides routine abdominal imaging to evaluate recurrences, stomach involvement should be evaluated, by gastric endoscopy, after pancreatic resection for pancreatic cancer.

Feczko et al.[10] mentioned five pathways of secondary involvement of the gastrointestinal tract: (1) direct invasion; (2) intraoperative seeding; (3) hematogenous metastases; (4) lymphatic metastases; and (5) intraluminal or intramural dissemination. Secondary involvement of the stomach from pancreatic carcinoma was reported to be due to dissemination, because the stomach is an adjacent organ.[11] In our patient, the gastric tumor was caused by blood-borne metastases, because the gastric tumor was localized in the submucosa.

There are no specific clinical symptoms related to gastric metastases. Caramella et al.[11] mentioned that a high frequency of asymptomatic cases (34.8%) was noted. The most frequent presenting symptom was bleeding, including occult bleeding, and a chronic occlusion syndrome accompanied by pain. Other reports have revealed nonspecific clinical manifestations, with weight loss, anorexia, abdominal discomfort, and nausea and vomiting being the most common manifestation.[4] In our patient, the clinical symptom was epigastric pain, which may have been due to a duodenal ulcer, because this symptom is relif after an ulcer has healed. Gastric endoscopy is an important diagnostic tool in evaluating gastric metastases. The morphological features of these lesions vary. Miyakawa et al.[12] stated that more than half of cases (57%) mimicked primary gastric carcinoma, and, of 69 cases, 18 cases (26%) were classified as Borrmann type IV. Indications for operation for these lesions are uncertain. Surgical intervention may be necessary for hemorrhage, obstruction, or perforation caused by the metastases. We performed resection of the lesion, because there was no evidence of local recurrence, and there were no other remote metastases, as confirmed by FDG-PET. To summarize, we have presented a case of gastric metastasis secondary to pancreatic adenocarcinoma, occurring 1 year after distal pancreatectomy.

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