Center Hospital East for further evaluation and treatment. The patient had no history of alcohol abuse.

Material and methods

The surgical specimen was fixed in 10% buffered formalin and submitted entirely for histology. The paraffin-embedded tissue were sectioned and stained with hematoxylin and eosin (H&E). Subsequently, tissue samples were stained immunohistochemically with the following monoclonal antibodies: cytokeratin (CK) 7 (1:100; Dako), CK20 (1:50; Dako), Muc-2 glycoprotein (1:100; Novocastra laboratories), and Muc-5AC glycoprotein (1:50; Novocastra laboratories).

Results

On physical examination, there were no abnormal abdominal findings. Other than slightly elevated γGTP (57 IU/l: normal 10–47) and blood glucose (107 mg/dl: normal 69–104) levels, all other laboratory tests, including the hematological profile, renal function, pancreatic enzymes, liver enzymes, electrolytes, and tumor markers (carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA)) were within normal limits.

On gastroduodenoscopy, the stomach appeared normal, but there was a villous polypoid tumor, about 3 cm in diameter, with a stalk in the second portion of the duodenum (Fig. 1). The major duodenal papilla was identified about 2 cm distal to the tumor. Computed tomography (CT) demonstrated a solid 40×35-mm tumor with expansive growth that occupied the lumen of the descending portion of the duodenum and showed slight attenuation with contrast medium. Tumoral extension toward the underlying pancreas was not detected. The CT also showed a series of pancreatic stones within the duct of the head of the pancreas. The distal side of the pancreatic duct was dilated and the parenchyma of the distal pancreas showed mild atrophy. Neither lymph node involvement nor distant metastasis was detected. Magnetic resonance cholangiopancreatography (MRCP) (Fig. 2) and the coronal view of magnetic resonance image (MRI) showed the relationship between the stones and the pancreatic duct more clearly. The series of stones was about 3 cm long; one end of the stones appeared to be positioned near the stalk of the tumor, and the other end was within the main pancreatic duct. The stones were suspected to be located within the dorsal pancreatic duct. MRCP also revealed a short ventral pancreatic duct; a communication between the dorsal and ventral pancreatic duct was not clearly identified. These findings suggested the existence of pancreas divisum.

Pathological examination of the preoperative biopsy specimen revealed a well-differentiated adenocarcinoma. With a presumptive diagnosis of adenocarcinoma of the duodenum or minor duodenal papilla and chronic pancreatitis, the patient had surgery. At laparotomy, because the tumor had a thick and broad stalk on palpation, it was suspected that the tumor might have invaded the duodenum or the underlying pancreas. Consequently, a subtotal stomach-preserving pancreaticoduodenectomy (SSpPD) was performed.

Macroscopic examination showed a villous polypoid tumor, 50×30×25 mm in size; the stalk was 15 mm in diameter. The tumor was located about 2 cm proximal from the major papilla, which was normal in size and shape. The cut surface showed that the dorsal pancreatic duct was

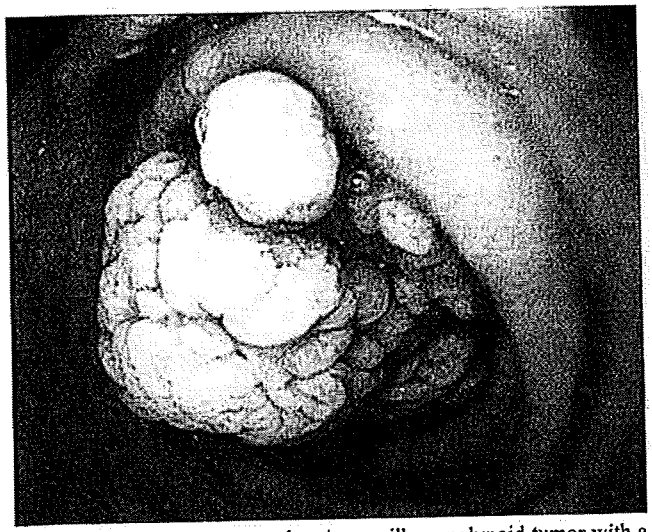


Fig. 1 Gastroduodenoscopy showing a villous polypoid tumor with a stalk in the second portion of the duodenum

Fig. 2 Magnetic resonance cholangiopancreatography (MRCP) showing a short ventral pancreatic duct (*white arrow*); the communication between the dorsal and ventral pancreatic ducts is not clearly identified. A series of stones (*white arrow head*) is seen in the dorsal pancreatic duct

obstructed by a series of stones, as had been demonstrated by the preoperative examinations (Fig. 3).

Microscopic examination showed that the main exophytic tumor was composed of eosinophilic tall columnar cells with oval and pseudostratified nuclei that were arranged in well-formed tubular pattern (Fig. 4a). The tumor was diagnosed as a well-differentiated tubular adenocarcinoma. The main tumor was limited to the mucosa and regarded as in-situ carcinoma without stromal invasion. At the tumor's stalk, muscular bundles similar to the sphincter of Oddi, which encircled the dorsal pancreatic duct, were present. These findings suggested that the tumor had arisen from the minor papilla and not from the duodenum. The adenocarcinoma cells spread through the sphincter bundles and the dorsal pancreatic duct; they replaced the normal pancreatic duct epithelium with intraductal carcinoma peripherally (Fig. 5a). Intraductal adenocarcinoma with micropapillary projection was observed in almost all areas of the dorsal pancreas, predominantly around the dorsal pancreatic duct. At the frontal edge of the intraductal spread, dysplastic epithelium and hyperplastic epithelium were observed (Figs. 5 and 6). At the cut end of the pancreas, the epithelium of the main pancreatic duct and the other branched ducts showed hyperplastic changes, which were considered to be reactive changes caused by tumor spread.

On immunohistochemical staining, both the main polypoid adenocarcinoma and the intraductal lesions showed the mixed positive pattern of CK7 and CK20. Muc-5AC was also multifocally positive both in the main tumor and the intraductal components. Muc-2 was negative except small number of cells in the base of the main tumor. The expression pattern for CK7, CK20, and Muc-5AC in the main tumor was maintained even in the ductal spreading area of the pancreas (Fig. 4).

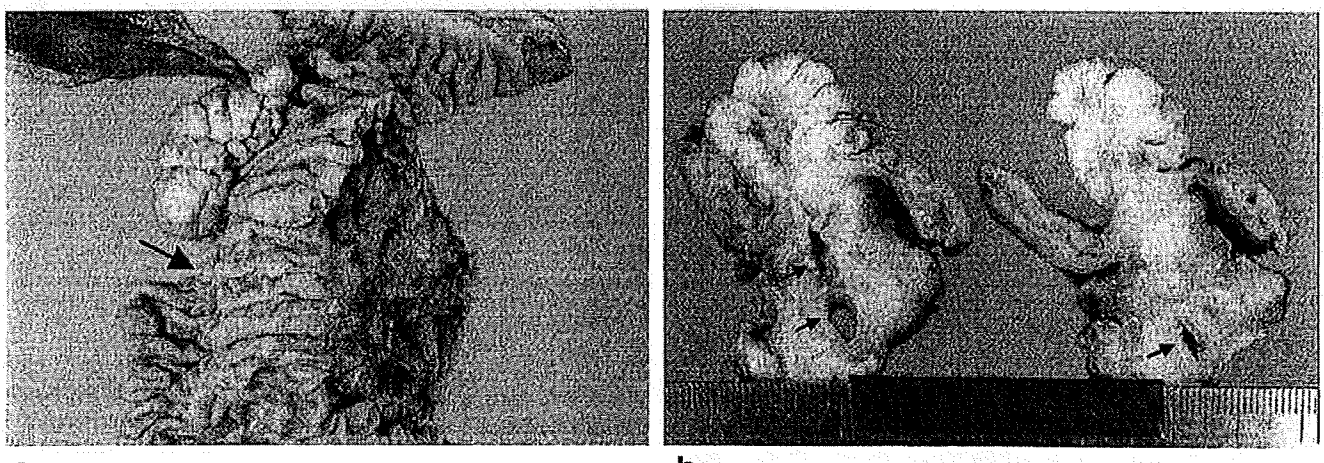
Chronic pancreatitis was found in the dorsal pancreatic parenchyma, with infiltration of inflammatory cells and fibrocollagenous tissue; the ventral pancreas was almost normal (Fig. 5a). The ventral pancreatic duct was short and narrow, and the epithelium of the ventral pancreatic duct did not include any carcinoma, dysplastic cells, or hyperplastic cells. These findings supported the presence of pancreas divisum. It is surprising to note that intraductal spread of carcinoma cells was observed in the small branches of the uncinate process, which anatomically belongs to the ventral pancreas, which was unaffected by pancreatitis (Figs. 5a and 6). About half of the uncinate process had carcinoma in situ. Neither lymphovascular invasion nor lymph node metastasis was observed.

The postoperative course was uneventful and the patient was discharged on the 13th postoperative day.

Discussion

The minor duodenal papilla is situated in the anterior duodenal wall, about 2 cm proximal to the major papilla [2, 16]. It primarily drains pancreatic fluid from the dorsal pancreas to the duodenum in the embryo [7].

Tumors of the minor duodenal papilla are uncommon, and few cases have been reported. Most reported cases have been submucosal benign tumors, such as carcinoid [12, 15, 19, 22, 23] and somatostatinoma [3, 13, 20]; only a single case of adenocarcinoma of the minor papilla has been previously reported [24]. Yamano et al. [24] reported a 77-year-old male with an ulcerating tumor, in which the dorsal pancreatic duct epithelium was partially replaced by carcinoma cells from the minor papilla; however, details of the pathological findings were not described. In contrast to our case, their case also had an intraductal papillary



a b

Fig. 3 a An exophytic polypoid tumor arising from the minor papilla. The major papilla (*arrow*) is normal in size and shape. b Cut section shows that the dorsal pancreatic duct was obstructed with a series of stones. (*arrows*; dorsal pancreatic duct with stones removed)

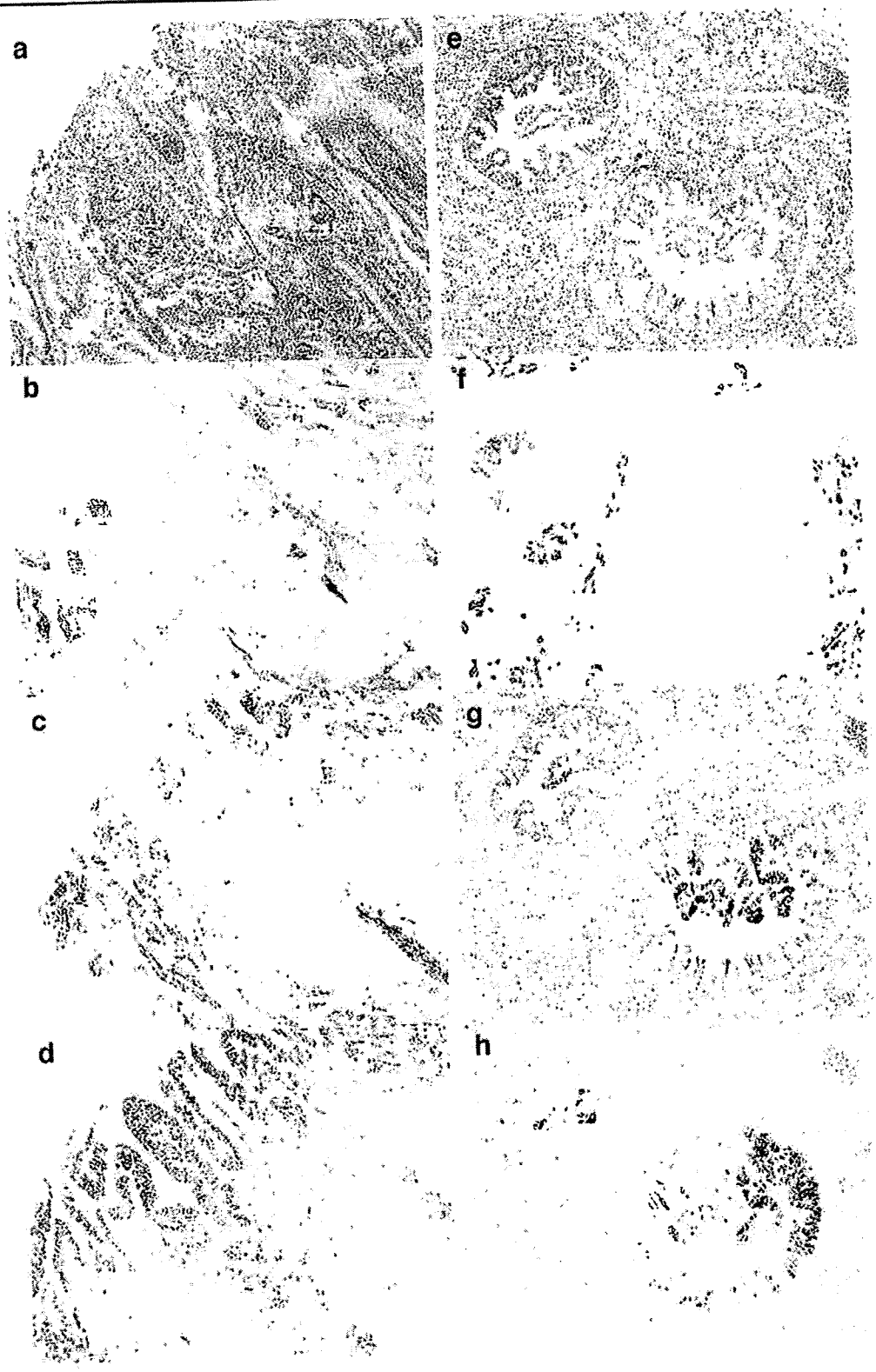


Fig. 4 a–d In-situ carcinoma of the main polypoid lesion (H&E, a) showing immunohistochemical positivity for CK7 (b), CK20 (c), and Muc-5AC (d) (×40). e–h Carcinoma in situ observed in the dorsal pancreatic duct (H&E, e) showing immunohistochemical positivity for CK7 (f), CK20 (g), and Muc-5AC (h) (×40)

adenoma with mucin hypersecretion in the cystically dilated branch duct in the head of the pancreas. Although the two tumors differed in their gross type, both cases had intraductal spread of the cancerous component. In the present case, however, carcinoma in situ had spread close to the cut end margin and also to the tiny peripheral branches without cystic dilatation.

In addition, our case had calcified stones located in the dorsal pancreatic duct. The majority of cases of pancreatic stones are secondary to chronic pancreatitis; however, the

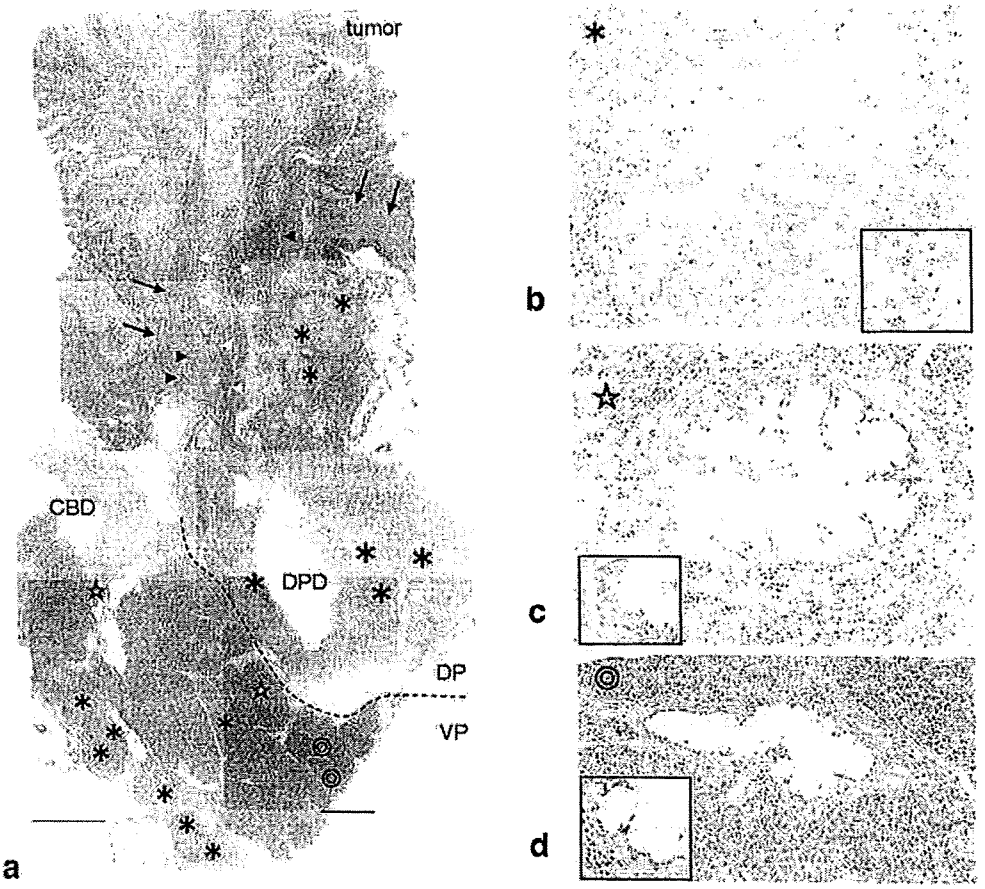


Fig. 5 a At the stalk of the tumor, muscular bundles (*black arrow* heads), which encircle the dorsal pancreatic duct (*white arrow heads*), are present. The carcinoma in situ has spread through the sphincter bundles to the branched duct around the dorsal pancreatic duct (DPD); dysplastic and hyperplastic epithelium are present peripherally (*black arrows*, muscular layer of the duodenum; *, carcinoma in situ; ☆, dysplastic epithelium; ◎, hyperplastic epithelium; *CBD*, common bile duct). Chronic pancreatitis is evident in the dorsal pancreas (DP), while the ventral pancreas (VP) appears almost normal. b Carcinoma in situ (*) (H–E×100). c Dysplastic epithelium (☆) (H–E×100). d Hyperplastic epithelium (◎) (H–E×100)

size, number, and distribution of stones vary by the type of pancreatitis [5, 10, 18]. In alcoholic chronic pancreatitis, there are numerous irregular small stones throughout the pancreas. On the other hand, in obstructive pancreatitis, the stone is usually large, solitary, and inside the lumen of the pancreatic duct. The pathogenesis of the stone is considered to be because of the stasis of pancreatic flow [17, 25]. With respect to stones in patients without a history of alcohol abuse, stagnation of pancreatic fluid as a consequence of the duct obstruction by a tumor might lead to development of stones, as in the present case.

The MRCP and MRI findings and the distribution of pancreatitis, which mainly affected the dorsal pancreas, suggested the existence of pancreas divisum. Pancreas divisum is a common congenital anomaly of the pancreas, which results from an abnormal fusion between the ventral and dorsal

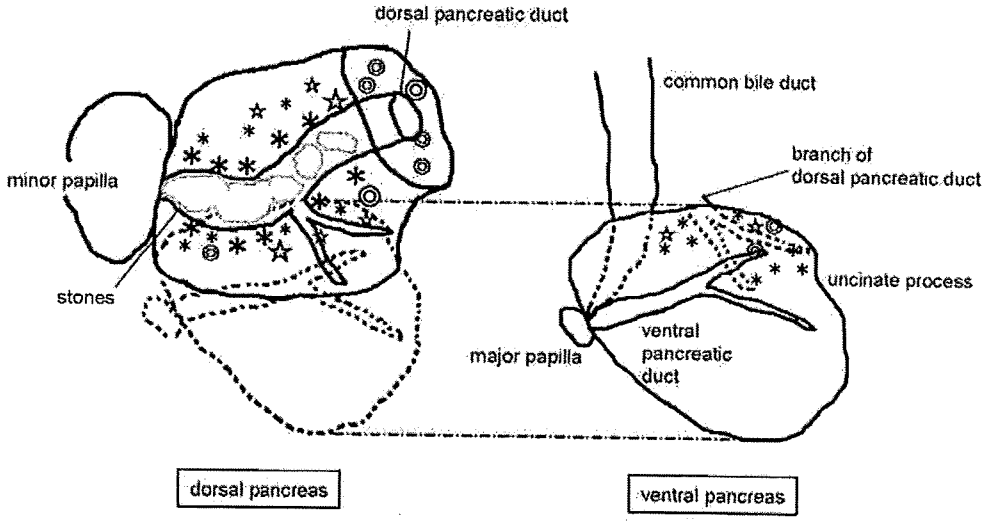


Fig. 6 Schematic distribution of carcinoma in situ (*), dysplastic epithelium (☆), and hyperplastic epithelium (◎). The dorsal and ventral pancreases are depicted separately for convenience. Carcinoma in situ is located predominantly near the dorsal pancreatic duct, and the dysplastic and hyperplastic epithelium is observed surrounding the carcinoma in situ. The branches of the uncinate process, which belongs to the ventral pancreas, are partially involved with cancerous spread

pancreatic ducts during fetal development [8]. It is divided into complete and incomplete types. In the complete type, there is no communication between the two ducts, whereas in the incomplete type, an inadequate communication exists between the two ducts. Pancreas divisum is strongly associated with pancreatitis, especially in alcoholic patients. Irrespective of the type of pancreas divisum, pancreatitis often occurs only in the dorsal pancreas, as was observed in this case. An interaction between a poorly functioning minor duodenal papilla and the increased flow of pancreatic juice caused by alcohol or food intake is thought to cause pancreatitis [8]. The presence of this anomaly in our patient may have promoted stasis of the pancreatic juice and the formation of the pancreatic stones.

In the present case, most of the intraductal carcinoma was limited to the dorsal pancreas, though some carcinoma was observed in the branches of the uncinate process, which is anatomically classified as being part of the ventral pancreas. In complete pancreas divisum, intraductal carcinoma in the dorsal pancreas never spreads to the ventral pancreas. Because intraductal components were observed in the uncinate branches, minor peripheral communications must have existed between the two ducts in our patient.

Pathologically, adenocarcinoma of the major papilla is classified into two types: intestinal and pancreatobiliary type, based on the epithelium of its origin [1, 9]. The former is derived from intestinal (duodenal) mucosa covering the papilla, whereas the latter is associated with pancreatobiliary epithelium lining the common channel and duct systems within the papilla. This classification is also supported by immunohistochemical staining such as cytokeratin and apomucin [26]. CK20 and Muc-2 are associated with the intestinal type, whereas CK7 and Muc-5AC expression is relatively specific for the pancreatobiliary type. Immunohistochemical staining in the present case showed the mixed positive expression for CK7 and CK20. This finding indicated that the tumor might arise from the transitional area between the intestinal mucosa covering the minor papilla and the dorsal pancreatic ductal epithelium. Moreover, the mixed positive pattern for CK7 and CK20 was observed uniformly from the main polypoid adenocarcinoma to the minute intraductal lesions, suggesting that the character of both components was equivalent. This fact supported that the intraductal components were extended from the main lesion.

On microscopic examination, the morphological feature of the intraductal carcinoma component was similar to that seen in intraductal papillary mucinous neoplasm (IPMN) of the pancreas or pancreatic intraepithelial neoplasia (PanIN). IPMN generally demonstrates grossly visible cystic lesions or exophytic masses (usually >1 cm in diameter) along with grossly visible papillae and luminal mucin production [6]. In the present case, the lesion suggesting IPMN was not detected in either radiological or macroscopical examination, and moreover, mucin was not observed on the cut surface of the specimen. In addition, the main polypoid tumor conclusively involved the minor papilla. The intraductal component, which was observed even in the tiny peripheral branches (<5 mm) with lowering the grade of the lesion distally, was in direct continuity with the main tumor. Taken together, it is consistent that the association of IPMN or PanIN was less likely, and the tumor originated from the minor papilla, then extended into the distal pancreatic duct.

The pathogenesis of our case likely involved the following factors: (1) the patient had a congenital, incomplete type of pancreas divisum that had been asymptomatic; (2) the tumor arose in the minor papilla and obstructed the dorsal pancreatic duct; (3) stagnation of the pancreatic fluid from the dorsal pancreas caused pancreatitis and the formation of calcified stones; (4) on the other hand, the intraductal tumor extended widely into the peripheral ducts, and some tumor components traveled through small communications between the dorsal and ventral pancreatic ducts, and eventually reached to the branches of the uncus, which was unaffected by pancreatitis.

It is interesting to note that, in this case, the intraductal component of the adenocarcinoma of the minor papilla extended along the pancreatic duct more than expected; it extended even beyond the minor communication between the dorsal and ventral pancreatic ducts of pancreas divisum, which was detected incidentally.

References

1. Albores-Saavedra J, Henson DE, Klimstra DS (2000) Malignant epithelial tumors of the ampulla. Tumor of the gallbladder, extrahepatic bile ducts, and ampulla of Vater. Atlas of tumor pathology. 3rd series. Washington DC, Armed Forces Institute of Pathology, pp 259–316
2. Baldwin WM (1911) The pancreatic ducts in man, together with a study of the microscopical structure of the minor duodenal papilla. Anat Rec 5:197–228
3. Borobia FG, Fabregat J, Jorba R, Poves I, Biondo S, Serrano T, Figueras J, Jaurrieta E (2001) Exocrine pancreatic insufficiency caused by a somatostatinoma of the minor and major duodenal papilla in a patient with neurofibromatosis. Eur J Surg 167:154–156
4. Fukuda A, Yazumi S, Sawada M, Seno H, Nabeshima M, Fujii H, Ikai I, Haga H, Chiba T (2005) Adenomyoma of the minor duodenal papilla. Gastrointest Endosc 61:475–479
5. Graziani R, Tapparelli M, Malagò R, Girardi V, Frulloni L, Cavallini G, Pozzi Mucelli R (2005) The various imaging aspects of chronic pancreatitis. JOP 6:73–88
6. Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, Biankin SA, Compton C, Fukushima N, Furukawa T, Goggins M, Kato Y, Klöppel G, Longnecker DS, Lüttges J, Maitra A, Offerhaus GJ, Shimizu M, Yonezawa S (2004) An illustrated consensus on the classification of pancreatic

intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol 28:977–987
7. Kamisawa T (2004) Clinical significance of the minor duodenal papilla and accessory pancreatic duct. J Gastroenterol 39:605–615
8. Kamisawa T, Tu Y, Egawa N, Tsuruta K, Okamoto A (2006) Clinical implications of incomplete pancreas divisum. JOP 7:625–630
9. Kimura W, Futakawa N, Zhao B (2004) Neoplastic diseases of the papilla of Vater. J Hepatobiliary Pancreat Surg 11:223–231
10. Lesniak RJ, Hohenwalter MD, Taylor AJ (2002) Spectrum of causes of pancreatic calcifications. Am J Roentgenol 178:79–86
11. Loew BJ, Lukens FJ, Navarro F, Roy M, Mattia A, Howell DA (2007) Successful endoscopic resection of a gangliocytic paraganglioma of the minor papilla in a patient with pancreas divisum and pancreatitis (with video). Gastrointest Endosc 65:547–550
12. Lowes JR, Rode J, Lee WR, Russell RC, Cotton PB (1988) Obstructive pancreatitis: unusual causes of chronic pancreatitis. Br J Surg 75:1129–1133
13. Malone MJ, Silverman ML, Braasch JW, Jin GL, Dayal Y (1985) Early somatostatinoma of the papilla of the duct of Santorini. Arch Surg 120:1381–1383
14. Nakamura T, Ozawa T, Kitagawa M, Takehira Y, Yamada M, Yasumi K, Tamakoshi K, Kobayashi Y, Nakamura H (2002) Endoscopic resection of gangliocytic paraganglioma of the minor duodenal papilla: case report and review. Gastrointest Endosc 55:270–273
15. Noda Y, Watanabe H, Iwafuchi M, Furuta K, Ishihara N, Satoh M, Ajioka Y (1992) Carcinoids and endocrine cell micronests of the minor and major duodenal papillae. Cancer 70:1825–1833
16. Ohta T, Nagakawa T, Kobayashi H, Kayahara M, Ueno K, Konishi I, Miyazaki I (1991) Histomorphological study on the minor duodenal papilla. Gastroenterol Jpn 26:356–362
17. Origuchi N, Kimura W, Muto T, Esaki Y (1998) Pancreatic mucin-producing adenocarcinoma associated with a pancreatic stone: report of a case. Surg Today 28:1261–1265
18. Ring EJ, Eaton SB Jr, Ferrucci JT Jr, Short WF (1973) Differential diagnosis of pancreatic calcification. Am J Roentgenol 117:446–452
19. Singh VV, Bhutani MS, Draganov P (2003) Carcinoid of the minor papilla in incomplete pancreas divisum presenting as acute relapsing pancreatitis. Pancreas 27:96–97
20. Stömmer PE, Stolte M, Seifert E (1987) Somatostatinoma of Vater's papilla and of the minor papilla. Cancer 60:232–235
21. Sugiyama M, Kimura W, Muto T, Yahagi N, Ichinose M, Miki K (1999) Endoscopic resection of adenoma of the minor papilla. Hepatogastroenterology 46:189–192
22. Waisberg J, de Matos LL, Waisberg DR, dos Santos HV, Fernezlian SM, Capelozzi VL (2006) Carcinoid of the minor duodenal papilla associated with pancreas divisum: case report and review of the literature. Clinics 61:365–368
23. Wang HY, Chen MJ, Yang TL, Chang MC, Chan YJ (2005) Carcinoid tumor of the duodenum and accessory papilla associated with polycythemia vera. World J Gastroenterol 11:3794–3796
24. Yamao K, Ohhashi K, Furukawa T, Mizutani S, Matsumoto S, Banno T, Fujimoto M, Hayakawa T (1998) Primary carcinoma of the duodenal minor papilla. Gastrointest Endosc 48:634–636
25. Zhang GW, Zhou J, Li CL, Huang YQ (2005) Diagnosis and treatment of pancreatolithiasis: report of 16 cases. Hepatobiliary Pancreat Dis Int 4:135–138
26. Zhou H, Schaefer N, Wolff M, Fischer HP (2004) Carcinoma of the ampulla of Vater: comparative histologic/immunohistochemical classification and follow-up. Am J Surg Pathol 28:875–882

J Hepatobiliary Pancreat Surg (2007) 14:586–589
DOI 10.1007/s00534-006-1218-x

Journal of HBP Surgery

Cystic endocrine tumor of the pancreas with an atypical multilocular appearance

Masatoshi Kajiwara[1], Naoto Gotohda[1], Masaru Konishi[1], Toshio Nakagohri[1], Shinichiro Takahashi[1], Motohiro Kojima[2], Takahiro Hasebe[3], and Taira Kinoshita[1]

[1] Department of Hepatobiliary Pancreatic Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan
[2] Pathology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan
[3] Surgical Pathology Section, Clinical Laboratory Division, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Abstract
A 46-year-old woman with epigastric pain was found to have a cystic tumor in the pancreas head on radiological examinations. The tumor was hypervascular, and its multilocular appearance resembled the "honeycomb" pattern of serous cystic tumor (SCT). The patient underwent surgery. The cut surface of the tumor showed a thick fibrous capsule with multiple cystic components, which contained necrotic tissue and brownish serous fluid, indicating an episode of hemorrhage. The cut surface of the tumor resembled solid-pseudopapillary tumor (SPT) on gross appearance. On immunohistochemical staining, the tumor cells showed diffuse and strong staining for synaptophysin (SYN), chromogranin A (CGA), and grimelius, and no staining for α 1-antitrypsin or CD10. We finally made a diagnosis of pancreatic endocrine tumor (PET). As PET sometimes shows an atypical multicystic appearance, immunohistochemical staining is mandatory for its correct diagnosis.

Key words Cystic endocrine tumor · Pancreas · Multilocular · Immunohistochemical staining

Introduction

Pancreatic endocrine tumor (PET) usually has a solid appearance, but it sometimes exhibits cystic components, especially in large lesions. Degenerative changes, such as hemorrhage and necrosis within the tumor during its growth, lead to the formation of cystic components.[1] If a cystic lesion is small enough, it is easy to make a correct diagnosis of PET. However, in cases in which the cystic components are intricate or occupy most of the tumor, it is sometimes difficult to distinguish it from other cystic tumors of the pancreas, such as solid-pseudopapillary tumor (SPT), mucinous cystic tumor (MCT), and serous cystic tumor (SCT).

This is a case report of a multicystic PET, which was preoperatively diagnosed as SCT and whose cut surface resembled SPT on gross appearance. We reached the correct diagnosis by performing immunohistochemical staining.

Case report

A 46-year-old woman presented with recurrent episodes of epigastric pain. She had had a history of bronchial asthma as a child, but was no longer on medication. She had no significant family history. On physical examination, no tumor was palpable in her abdomen. Laboratory test results, including amylase level, liver function, and carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) levels, were all within normal limits. Abdominal ultrasonography (US) revealed a well-circumscribed, multilocular cystic mass in the head of the pancreas that measured up to 6 cm in diameter. Endoscopic ultrasound examination (EUS) showed the structure of the tumor more clearly, and multiple cysts of variable size resembled the "honeycomb" appearance of SCT (Fig. 1a). Computed tomography (CT) demonstrated a 6-cm mass in the head of the pancreas; the mass was encapsulated by a thick wall, with calcification in the precontrast phase (Fig. 1b,c). The wall, septum, and solid components of the tumor were highly enhanced by contrast medium (Fig. 1d,e). Neither liver metastasis nor lymph node involvement around the pancreas was detected. After the CT examination, a skin rash emerged on her whole body, so further examination using contrast medium (angiography or endoscopic retrograde cholangiopancreatography [ERCP]) was not performed. On magnetic resonance imaging (MRI), the tumor showed heterogeneous low intensity on T1-weighted images

Offprint requests to: N. Gotohda
Received: November 17, 2006 / Accepted: December 27, 2006

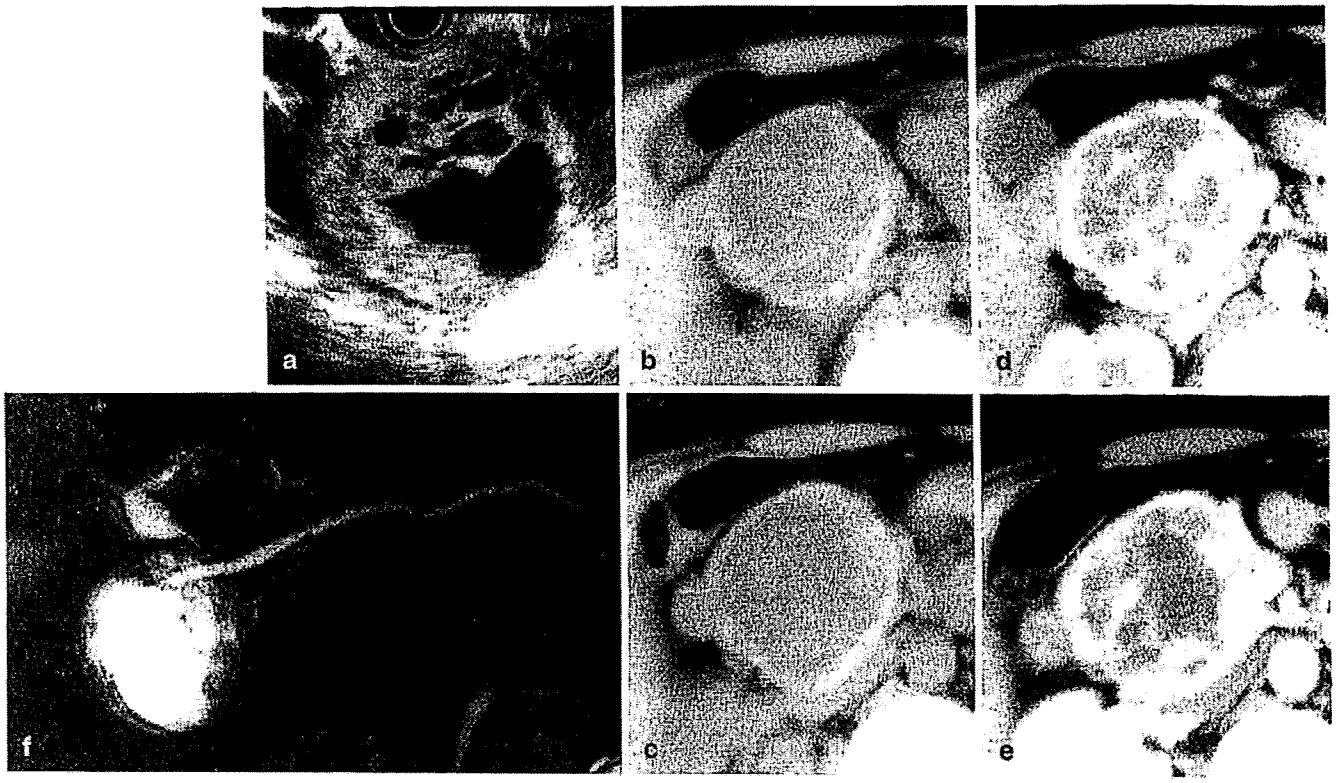


Fig. 1. **a** Endoscopic ultrasound (EUS) examination showed multiple cysts of variable size, which resembled the "honeycomb" appearance of a serous cystic tumor (SCT). **b, c** Computed tomography (CT) demonstrated a 6-cm mass in the head of the pancreas, encapsulated by a thick wall, with calcification in the precontrast phase. **d, e** On CT, the wall, septum, and solid components of the tumor were highly enhanced by contrast medium. **f** Magnetic resonance cholangiopancreatography (MRCP) revealed that the main pancreatic duct (MPD) and common bile duct (CBD) were compressed by the tumor and showed mild dilatation distally

and spotty high signal intensity, in concordance with the cystic components, on T2-weighted images. Magnetic resonance cholangiopancreatography (MRCP) revealed that the main pancreatic duct (MPD) and common bile duct (CBD) were compressed by the tumor and showed mild dilatation distally (Fig. 1f).

With a presumptive diagnosis of SCT, the patient underwent sub-total stomach-preserving pancreaticoduodenectomy (SSpPD). The postoperative course was uneventful and she was discharged on the fourteenth postoperative day. Six months after the surgery, she is alive without any evidence of recurrence.

Macroscopically, the tumor was round and elastic hard, measuring 7.5 × 7.0 × 6.5 cm. The cut surface showed a thick fibrous capsule with multiple cystic components, which contained necrotic tissue and brownish serous fluid, indicating an episode of hemorrhage (Fig. 2a). The gross appearance of the cut surface of the tumor resembled an SPT.

Microscopic examination revealed that the tumor was extensively vascularized, with areas of hemorrhage and necrosis, and a moderate amount of stroma. The tumor cells were medium-sized and their nuclei were round and uniform. No mitosis was detected. The tumor cells were arranged mainly in a trabecular pattern. In some areas, however, the tumor cells were separated by stroma and showed a pseudopapillary-like pattern (Fig. 2b,c). There was no lymph node metastasis around the tumor. Neither extracapsular invasion nor blood vessel invasion was detected. For discrimination between SPT and PET, immunohistochemical examination was performed. The tumor cells showed diffuse and strong staining for synaptophysin (SYN; Fig. 2d), chromogranin A (CGA; Fig. 2e), and grimelius (Fig. 2f), and weak staining for AE1/AE3. However, there was no staining for α 1-antitrypsin or CD10 (Fig. 2g). The morphologic appearance and immunohistochemical profile were compatible with PET. To evaluate the malignant potential of this tumor, we checked the MIB-1 index, and it was less than 1%.

Discussion

Pancreatic endocrine tumor (PET) usually shows a solid pattern, but it sometimes exhibits cystic components,

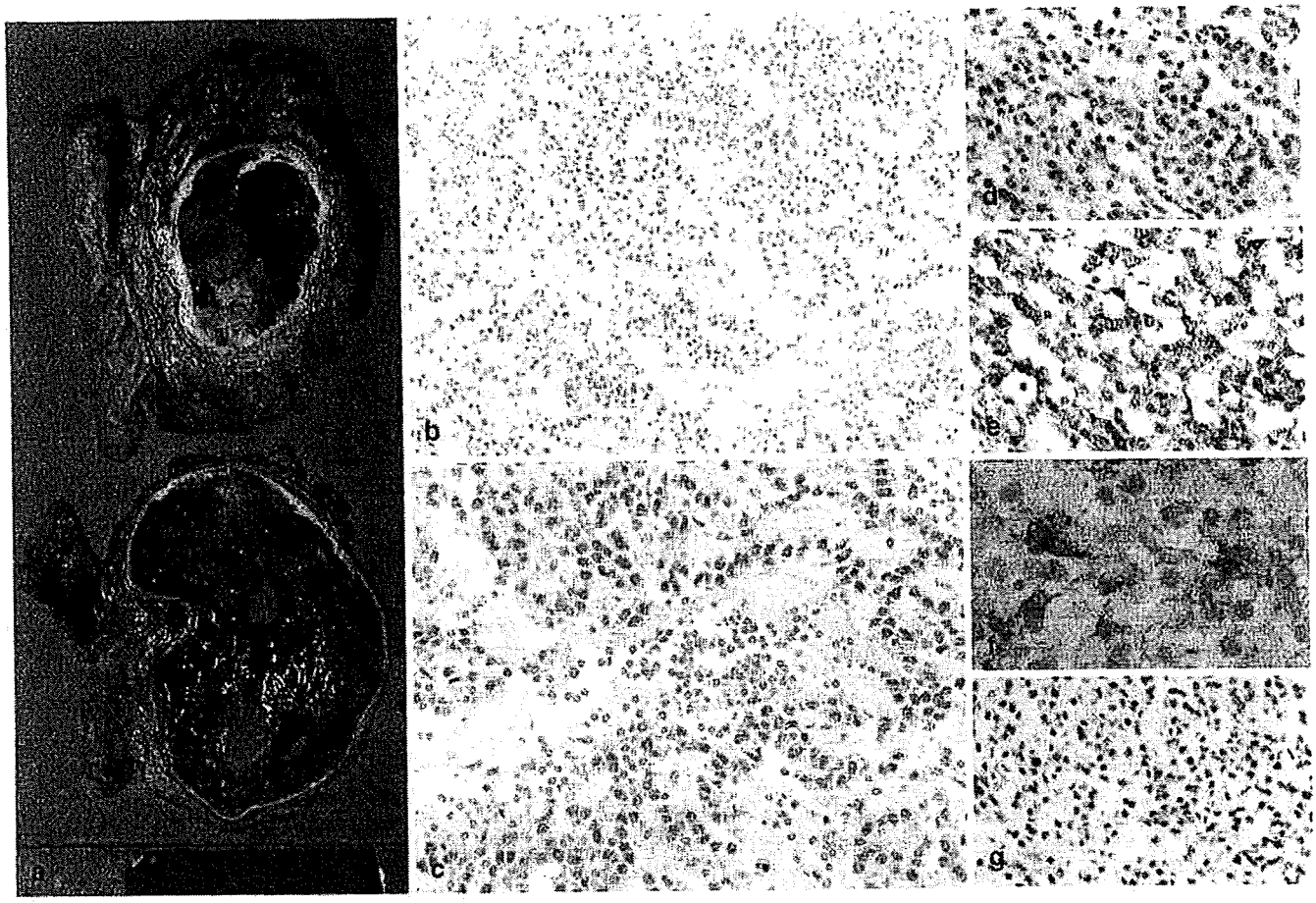


Fig. 2. **a** Macroscopically, the cut surface of the tumor showed a thick fibrous capsule with multiple cystic components. Its gross appearance resembled a solid-pseudopapillary tumor (SPT). **b, c** Microscopically, the tumor cells were arranged in a trabecular pattern. In some areas, however, the tumor cells showed a pseudopapillary-like pattern. **d, e, f, g** On immunohistochemical staining, the tumor cells showed diffuse and strong staining for synaptophysin (**d**), chromogranin A (**e**), and grimelius (**f**),and no staining for CD10 (**g**). **b** H&E, ×100; **c** H&E, ×200; **d** ×200; **e** ×200; **f** ×400; **g** ×200

especially in large lesions. The formation of cystic components within PET seems to be due to hemorrhage and necrosis of the tumor during its growth.[1] These degenerative changes are sometimes accompanied by the formation of a fibrous capsule around the tumor, which reduces its vascularization and promotes ischemic changes.[2]

Most cystic PETs are reported to be nonfunctioning tumors which do not produce enough hormone to produce clinical symptoms, whereas functioning tumors such as gastrinomas and insulinomas are usually detected at a small size because of their characteristic clinical manifestations.[2,3]

Cystic PET, of course, has the same radiological characteristics as the common solid type of PET, such as hypervascularity and the presence of calcification. Furthermore, cystic PET is reported to have unique radiographic findings such as thickening of the cyst wall and irregularity of the inner surface.[4] These structures are well-enhanced on post-contrast CT or MRI. The cystic components of PET vary in size and number. They are sometimes unilocular and sometimes multilocular. If the cystic lesion is small enough, it is possible to reach the correct diagnosis of PET from its characteristic radiological appearance, as mentioned above. However, when it shows a complicated cystic pattern, cystic PET can be misdiagnosed as other cystic tumors of the pancreas, such as SPT, SCT, and MCT.

Ligneau et al.[5] reported that 7 of 13 cystic PETs showed a microcystic appearance, and 2 of the 7 were diagnosed as SCT preoperatively. Gerke et al.[6] reported a case of a nonfunctioning PET that had the typical microcystic "honeycomb" appearance of SCT on preoperative imaging. Similarly, our initial diagnosis in the present patient was SCT, as the tumor was hypervascular, and its multilocular appearance resembled the "honeycomb" pattern of SCT. The thickness of the wall of the tumor, however, was not typical of SCT, which, in retrospect, we should have noted. Some other case reports have also indicated difficulties in making a diag-

nosis of cystic pancreatic tumors preoperatively owing to the variation in their appearance.[7,8]

The gross appearance of the tumor in our patient mimicked that of SPT. The tumor had a thick fibrous capsule, consisted of solid and cystic components, and contained necrotic tissue and brownish serous fluid, which indicated a hemorrhagic episode. It is thought that degenerative changes, such as necrosis and hemorrhage, occurred multifocally within the tumor during its growth, followed by the formation of the cystic components.

Microscopically, round, uniform tumor cells were arranged in a trabecular pattern. As they were separated by loose fibrous stroma, they displayed a pseudopapillary-like pattern in some areas. SPT often shows endocrine differentiation, and is sometimes positive for endocrine markers such as neuron-specific enolase (NSE) and SYN.[9] On immunohistochemical staining to differentiate PET from SPT, Notohara et al.[9] reported that CD10 and neuroendocrine markers, such as CGA and SYN, were useful. They reported that all SPTs they investigated had strong reactivity for CD10, whereas 95% of the PETs were negative or only focally positive for CD10. All the SPTs were negative for CGA. On the other hand, all the PETs demonstrated positive reactivity for CGA.

In our patient, the tumor cells showed diffuse and strong staining for CGA, and no staining for CD10. Thus, we finally made a diagnosis of cystic PET. We did not perform immunohistochemical staining for insulin, glucagon, somatostatin, or pancreatic polypeptide. According to the recent World Health Organization (WHO) criteria,[10] this case was classified as well-differentiated endocrine tumor with uncertain behavior, because it did not have any lymph node metastasis, local invasion, blood vessel invasion, or mitosis, and its MIB-1 index was less than 2%, but the size of the tumor was greater than 2cm. Our patient will need close follow-up to monitor for recurrence.

We should be alerted that PET sometimes shows a multicystic appearance mimicking other pancreatic cystic tumor entities. Immunohistochemical staining is mandatory for the correct diagnosis of PET.

References

1. Davtyan H, Nieberg R, Reber HA. Pancreatic cystic endocrine neoplasms. Pancreas 1990;5:230–3.
2. Iacono C, Serio G, Fugazzola C, Zamboni G, Bergamo Andreis IA, Jannucci A, et al. Cystic islet cell tumors of the pancreas. A clinico-pathological report of two nonfunctioning cases and review of the literature. Int J Pancreatol 1992;11:199–208.
3. Buetow PC, Parrino TV, Buck JL, Pantongrag-Brown L, Ros PR, Dachman AH, et al. Islet cell tumors of the pancreas: pathologic-imaging correlation among size, necrosis and cysts, calcification, malignant behavior, and functional status. AJR Am J Roentgenol 2002;165:1175–9.
4. Takeshita K, Furui S, Makita K, Yamauchi T, Irie T, Tsuchiya K, et al. Cystic islet cell tumors: radiologic findings in three cases. Abdom Imaging 1994;19:225–8.
5. Ligneau B, Lombard-Bohas C, Partensky C, Valette PJ, Calender A, Dumortier J, et al. Cystic endocrine tumors of the pancreas: clinical, radiologic, and histopathologic features in 13 cases. Am J Surg Pathol 2001;25:752–60.
6. Gerke H, Byrne M, Xie HB, Paulson EK, Tyler DS, Baillie J, et al. A wolf in sheep's clothing: a non-functioning islet cell tumor of the pancreas masquerading as a microcystic (serous cystic) adenoma. JOP 2004;5:225–30.
7. Fujiwara H, Ajiki T, Fukuoka K, Mitsutsuji M, Yamamoto M, Kuroda Y. Macrocystic serous cystadenoma of the pancreas. J Hepatobiliary Pancreat Surg 2000;7:92–6.
8. Seki M, Ninomiya E, Aruga A, Yamada K, Koga R, Saiura A, et al. Image-diagnostic features of mature cystic teratomas of the pancreas: report on two cases difficult to diagnose preoperatively. J Hepatobiliary Pancreat Surg 2005;12:336–40.
9. Notohara K, Hamazaki S, Tsukayama C, Nakamoto S, Kawabata K, Mizobuchi K, et al. Solid-pseudopapillary tumor of the pancreas: immunohistochemical localization of neuroendocrine markers and CD10. Am J Surg Pathol 2000;24:1361–71.
10. Heitz PU, Komminoth P, Perran A, Klimstra DS, Dayal Y, Bordi C, et al. Tumor of the endocrine pancreas. In: Delellis RA, Lloyd RV, Heitz PU, Eng C, editors. World Health Organization classification of tumors: pathology and genetics of tumors of endocrine organs. Lyon: IARC; 2004. p. 175–208.

Adjuvant and Neoadjuvant Therapy of Gastric Cancer: A Comparison of Three Pivotal Studies

Takeshi Sano, MD

Corresponding author
Takeshi Sano, MD
Gastric Surgery Division, National Cancer Center Hospital,
5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.
E-mail: tksano@ncc.go.jp

Current Oncology Reports 2008, **10**:191–198
Current Medicine Group LLC ISSN 1523-3790

In the past, the role of adjuvant therapy for gastric cancer was indefinite. However, three large, randomized controlled trials have recently shown the survival benefit of adjuvant therapy over surgery alone: the American INT 0116 trial, with adjuvant chemoradiation therapy; the European MAGIC trial, with perioperative combination chemotherapy; and the Japanese ACTS-GC trial, with adjuvant monotherapy. Because the patient populations and surgical approaches are considerably different among these trials, it is not sensible to simply compare survival rates to determine the best modality. In the time since these pivotal trials, various innovative studies have been planned and launched to evaluate treatment factors including modality (chemotherapy or chemoradiation), timing (before and/or after surgery), and different surgical extent (D1 or D2 lymphadenectomy). Because the East and West have different backgrounds and treatments for localized gastric cancer, each region should design its own clinical trial to determine the best evidence-based treatment regimens.

Introduction

Adjuvant therapy aims to improve survival by eliminating residual micrometastatic disease after curative resection of solid tumors. Gastric cancer has long been a focus of adjuvant studies; however, numerous past trials failed to prove the benefit of adjuvant therapy. Although some meta-analyses showed statistically significant superiority of adjuvant chemotherapy, they could not provide clinically significant conclusions due to the heterogeneity in therapeutic regimens, disease stages, and quality of surgery among the studied trials [1,2]; all phase 3 trials thus needed a control arm of surgery alone to produce evidence. The absence of a pivotal trial in adjuvant therapy for gastric cancer could be attributed to two reasons: 1) the absence of powerful treatment regimens to improve survival, and 2) the difficulty in conducting a large-scale, randomized controlled trial with sufficient statistical power for this disease.

Recently, three different modalities of adjuvant therapy for localized gastric cancer were proven to improve survival in three large-scale, randomized controlled trials conducted in three different regions in the world. These trials, the SWOG 9008/INT 0116 trial (INT 0116) of adjuvant chemoradiation in the United States [3], the MAGIC trial of perioperative three-agent chemotherapy in Europe [4••], and the ACTS-GC trial of adjuvant S-1 monotherapy in Japan [5••] have led to a new phase in this field of study.

Because these studies have different patient populations and surgical approaches, cross-trial comparisons of the survival results are not easy. In this review, these trials are carefully compared with special reference to the patient selection and the role of surgery. Currently active clinical trials and future directions are also discussed.

Overview of the Three Trials

The INT 0116 trial

The eligibility criteria for the INT 0116 study included stage IB through IV M0 adenocarcinoma of the stomach or gastroesophageal junction, with registration occurring 20 to 41 days after complete resection with free resection-line involvement. Of the 603 patients registered between 1991 and 1998, 556 were eligible and randomly assigned to surgery only (n = 275) or to surgery plus chemoradiotherapy (n = 281). The adjuvant regimen consisted of 5-fluorouracil (5-FU) (425 mg/m^2) plus leucovorin (20 mg/m^2) for 5 days, followed by a total of 45-Gy radiation given for 5 weeks with modified doses of 5-FU/leucovorin, and two 5-day cycles of 5-FU (425 mg/m^2) plus leucovorin (20 mg/m^2). Chemoradiotherapy was completed as planned in 64% of patients; it was stopped in 25% because of toxic effects or patient declination. Three patients (1%) died of toxic effects.

More than half the tumors were located in the antrum, and about 20% were in the cardia. Sixty-nine percent of the tumors were T3 or T4, and 85% had nodal metastases. The review of the surgical records of 552 patients showed that, although the study protocol had recommended D2 lymphadenectomy, the majority underwent limited resection (54% D0, 36% D1, 10% D2). With a median follow-up of 5 years, the median survival time and the 3-year survival rates of the surgery and surgery-plus-chemoradiation groups were 27 months (41%) and 36 months (50%), respectively. The first site of recurrence was more local-regional in the surgery-only group than in the adjuvant group.

The MAGIC trial

The eligibility criteria for the MAGIC trial included stage II or higher M0 adenocarcinoma of the stomach or lower third of the esophagus that was deemed resectable. Between 1994 and 2002, 503 patients were randomly assigned to surgery alone (n = 253) or to perioperative chemotherapy and surgery (n = 250). The chemotherapy consisted of three preoperative and three postoperative cycles of ECF: epirubicin (50 mg/m^2) plus cisplatin (60 mg/m^2) on day 1 and a continuous intravenous infusion of 5-FU (200 mg/m^2) for 21 days. Of the 237 patients who started preoperative chemotherapy, 215 (90.7%) completed it, and 209 of this subset proceeded to surgery. Postoperative chemotherapy was started in 137 patients and was completed in 104 patients (41.6% of the chemotherapy group).

Surgery was performed in 91.6% of the chemotherapy group and in 96.4% of the surgery group. Resection was curative in 69.3% of the chemotherapy group and 66.4% of the surgery group. The extent of lymphadenectomy was not specified in the protocol and was decided by the surgeon. The postoperative mortality rates were similar between the two groups (5.6% and 5.9%). In the surgery group, 63.2% of tumors were T3 or T4, and 73.1% had lymph node metastases. In the chemotherapy group, the tumor diameter was smaller, the proportion of T1 and T2 was greater, and the proportion of N0 and N1 was greater than in the surgery group, suggesting the downstaging effect of preoperative chemotherapy.

With a median follow-up of 47 to 49 months, the overall and progression-free survival rates in the chemotherapy group were significantly better than those in the surgery group. The 5-year survival rates were 36.3% in the chemotherapy group and 23.0% in the surgery group. Both local and distant recurrences were more frequently seen in the surgery group.

The ACTS-GC trial

The eligibility criteria for the ACTS-GC trial included stage II (excluding T1), IIIA, or IIIB adenocarcinoma of the stomach, after D2 or more extensive curative surgery, with no tumor cells in the peritoneal lavage cytology; patients were also no older than 80 years of age. Between 2001 and 2004, 1059 patients were registered from 109 high-volume hospitals in Japan and were randomly assigned to surgery only (n = 530) or to adjuvant chemotherapy (n = 529). The chemotherapy consisted of 6-week cycles of S-1 (an orally active fluoropyrimidine [6–8]; 80 mg/m^2 for 4 weeks followed by 2-week rest) for 1 year starting within 6 weeks postoperatively. This regimen was continued for at least 3 months in 87.4% of patients, for 6 months in 70.8%, and for 12 months in 65.8%. Dose modification due to toxicity was necessary in 42.4% of patients. The tumors were predominantly located in the distal stomach; 58% were treated by distal gastrectomy. Forty-six percent of the tumors were T3 or T4, and 89% had lymph node metastasis.

The study was designed to compare the 5-year overall survival, but the first interim analysis with a median follow-up of 2 years showed a significant difference in overall and relapse-free survival in favor of the chemotherapy group, and the trial was discontinued. In the published data, with a median follow-up of 2.9 years, the 3-year overall survival rates were 80.1% in the chemotherapy group and 70.1% in the surgery group. Fewer relapses in peritoneum and lymph nodes were observed in the chemotherapy group. Subgroup analyses showed no interaction between any studied variables.

Comparison of the Three Trials

Patient population

Curability

The patient population was essentially different between the MAGIC trial and the other two trials. MAGIC recruited cases deemed to be resectable, whereas the other two studies included only patients after curative gastrectomy. It has been well established that R0 resection without gross or microscopic residual disease is one of the most important prognostic determinants of gastric cancer [9,10].

Curability of gastric cancer without apparent distant metastasis largely depends on peritoneal dissemination. Staging laparoscopy with biopsy is the only method available to diagnose this before definitive surgery. In the MAGIC trial, laparoscopy was listed as a staging method but did not seem to have been employed in many patients: in 28% of the patients assigned to the surgery group, the operation turned out to be noncurative at laparotomy, and half of these individuals underwent nonresectional surgery.

Contamination of noncurative cases is inevitable in neoadjuvant trials but should be avoided with every effort. It is especially important to exclude individuals with peritoneal metastasis that is most refractory to chemotherapy. In current ongoing trials for neoadjuvant therapy, staging laparoscopy is usually mandatory to exclude peritoneal disease and is useful to select patients who may truly benefit from the treatment [11•].

Tumor stage

In the INT 0116 and ACTS-GC trials, only patients with pathologically confirmed stages after curative resection were recruited. More T3/T4 tumors were included in INT 0116 (69%) than in ACTS-GC (46%), but lymph node metastasis was less frequently detected in INT 0116 (85%) than in ACTS-GC (89%). It is well established that incidence and extent of nodal metastasis closely correlate with T stage of the primary tumor [12]; therefore, the above observation may appear contradictory. This may be explained by the fact that lymphadenectomy and postoperative nodal retrieval are more extensively performed in Japan; thus, small nodal disease possibly overlooked in the US trial could be detected.

In the MAGIC trial, it is difficult to determine the exact proportions of T and N stages of gastric cancer from the published data, partly because they were presented together with esophageal cancers and partly because there are several missing or "unknown" data. Nodal status is available in 156 of 187 gastric cancer patients in the surgery group, and only 114 (73%) had nodal metastasis, which is considerably lower than the other two trials (85% for INT 0116 and 89% for ACTS-GC). However, this is likely to be an underestimation because nonresectable cases with high probability of nodal metastasis were not included in this calculation.

A notable eligibility criterion used in ACTS-GC was the negative result of peritoneal cytology. Free cancer cells detected in the lavage fluid at the beginning of laparotomy or staging laparoscopy are a strong indicator of poor prognosis [13•], and the Japanese Classification [14] includes this as a determinant of the disease stage (ie, a tumor with positive cytology is staged as IV regardless of the T or N status). Exclusion of patients with positive cytology facilitates selection of patients with minimal residual disease who thus may benefit from adjuvant chemotherapy.

In all, Japanese patients in ACTS-GC were a highly selective population with the best prognosis among the three trials. Patients in MAGIC had the poorest prognosis at the time of registration because a considerable proportion had noncurative, even unresectable, disease. American patients in INT 0116 had more advanced T3/T4 disease than the Japanese patients but with better prognosis than the MAGIC population because they had undergone at least grossly curative resection.

Tumor site and type of surgery

Today, there is a remarkable difference between the East and the West in regard to the anatomical location of gastric cancer; in the West, a prominent shift to the proximal stomach exists [15,16]. Nevertheless, most tumors in the INT 0116 trial were located in the distal stomach, and 60% of the patients underwent distal gastrectomy. It is interesting that this rate of distal gastrectomy was very similar to that in the Japanese ACTS-GC trial (58%).

The MAGIC trial initially recruited only patients with gastric cancer, but extended the inclusion criteria to those with adenocarcinoma of the lower esophagus in the last 3 of the 8 accrual years. Fourteen percent of the tumors in the trial were lower esophageal cancer, and 22% of the patients in the surgery group underwent esophagogastrectomy. Of the other 146 gastric resections in this group, distal gastrectomy accounted only for 37%, indicating the predominance of proximal tumors in the trial.

The predominance of distal tumors in ACTS-GC and that of proximal tumors in MAGIC appears to reflect the general background of the disease in each region, although the patients in the INT 0116 trial may not represent American gastric cancer patients. The strict eligibility criteria of curative gastrectomy may have excluded many proximal or esophagogastric junction tumors which are, in general, locally more aggressive than distal tumors [17].

Lymphadenectomy

In adjuvant trials, surgery does not draw much attention because it is not a tested variable; rather it is a constant that is supposed to be the same or alike between the compared arms. However, when the results of separate studies are compared or combined for meta-analysis, the quality of surgery should be considered with great attention. In most solid tumors, including gastric cancer, surgery still plays the key role for cure, and the extent of surgery can easily alter the volume of residual tumor burden. If an adjuvant therapy aims at the systemically scattered cancer cells, the difference of surgery does not much matter. However, if the local residual disease is an important prognostic determinant to be targeted by adjuvant therapy, as in INT 0116, extent of surgery should be strictly controlled because it will directly affect the trial end points.

In the ACTS-GC trial, great attention was given to the quality assurance of surgery. Only high-volume centers participated in the study, the extent of lymphadenectomy was carefully reviewed, and the minimum requirement of D2 was confirmed before registration. In a D2 lymphadenectomy, the perigastric (N1) nodes and those along the branches of the celiac artery (N2) are completely removed [14].

In the INT 0116 trial, the operative records were reviewed in terms of lymphadenectomy, and it was found that the vast majority (90%) of patients had undergone limited lymphadenectomy [18]. Considering the high incidence of pathological nodal involvement in these patients (85%), microscopic disease must have remained in the nodes around the celiac artery in a considerable proportion of cases. In the subset analysis of the long-term results, chemoradiation did not improve survival of patients undergoing D2 lymphadenectomy [19]. Thus, the positive results of this study could be interpreted to mean that chemoradiation therapy was effective in eradicating the residual local disease, thereby reducing local recurrence and subsequent systemic metastasis.

Table 1. Survival data of three pivotal trials

	INT 0116	MAGIC*	ACTS-GC
Surgery group			
3-year overall survival, %	41	31	70.1
3-year relapse-free survival, %	31	25	59.6
Chemo(radiation) group			
3-year overall survival, %	50	44	80.1
3-year relapse-free survival, %	48	40	72.2
Hazard ratios between arms			
Death	0.74	0.75	0.68
Progression	0.66	0.66	0.62

*Three-year survival rates in MAGIC trial were not shown (Cunningham et al. [4••]). The listed figures were estimations obtained from the survival curves presented.

In the MAGIC trial, the extent of lymphadenectomy was at the surgeon's discretion. Cunningham et al. [4••] reported that D2 lymphadenectomy was performed more frequently than D1 (96 and 50 cases, respectively, in the surgery group); however, this cannot be accepted at face value. First, these terms were used inaccurately (the researchers incorrectly termed "D1" as denoting limited lymph node dissection, and "D2" as denoting extended lymph node dissection), suggesting that a precise review of operative records, such as in the INT 0116 study, did not occur. Second, D2 lymphadenectomy, in its properly defined context, was not the standard of surgery in Europe at the time of the trial. Extremely high hospital mortality rates following D2 lymphadenectomy in both the Dutch D1/D2 trial and the British D1/D2 trial (10% and 13%, respectively) had been recently published (1995 and 1996) [20,21] at the time of MAGIC trial accrual (between 1994 and 2002); therefore, surgeons participating in the MAGIC trial had no strong reason to perform this dangerous surgery, especially after intensive chemotherapy. Indeed, the operative mortality of the MAGIC trial (5.4% in the chemotherapy group and 5.9% in the surgery group) was even lower than that of D1 group in the British D1/D2 trial (6.5%). Therefore, it seems inappropriate to consider that the surgery was more radical in MAGIC than in INT 0116 [22].

Survival

The survival data of the three trials are summarized in Table 1. Following publication of the INT 0116 and MAGIC trial data, many discussions have arisen regarding which therapy—adjuvant or perioperative—is superior in terms of survival [23]. However, this comparison requires special attention because these trials had essentially different populations in terms of curability and disease stages, as discussed above. Despite the difference in the survival rates between the two trials, the hazard ratios for both death and progression between the surgery and treatment arms were exactly the same.

There was a strikingly large difference in baseline survival between the Japanese study and the other two trials. The 3-year overall and relapse-free survival rates in the surgery group of ACTS-GC were almost twice as high as those in INT 0116 and MAGIC. Again, this should be attributed to the population differences discussed above. A more aggressive surgical approach in Japan may also have contributed to this survival difference. However, the 3-year survival of gastrectomy plus chemoradiation in INT 0116 (50%), which could be considered a result of optimal local therapy, was still far inferior to that of the Japanese surgery-only group (70.1%); the difference in local control alone cannot explain such a large survival difference.

Other Recently Concluded and Currently Ongoing Studies

In the time since the three pivotal studies discussed previously, other clinical studies in the United States, Europe, and East Asia have recently concluded or are ongoing (Table 2).

Studies in the United States

Following INT 0116, adjuvant chemoradiotherapy has become a standard treatment option in the United States; all ongoing clinical trials for localized gastric cancer now include chemoradiation. In a phase 3 trial (CALGB-80101), the chemoradiation regimen used in the INT 0116 trial is being compared with one in which the ECF regimen of the MAGIC trial is used rather than 5-FU/leucovorin [24].

Neoadjuvant chemoradiation is a new subject drawing great attention. A phase 2 trial (RTOG 9904) in a cooperative study setting tested a regimen consisting of 5-FU/leucovorin/cisplatin induction followed by concurrent 45-Gy radiation and 5-FU, as well as weekly paclitaxel prior to surgical resection. Results showed pathological complete response in 26% and favorable survival of responders [11•]. Other chemotherapeutic regimens currently being evaluated in combination with radiation include capecitabine and oxaliplatin (SWOG-S0425) [25].

Table 2. Currently active phase 3 trials on (neo)adjuvant therapy for gastric cancer

Study	Country	Patients, *n*	Disease	Therapeutic modes
CALGB-80101 [24]	USA	824	Stage Ib–IV M0	Surgery + chemoradiation (RT + 5-FU/leucovorin) vs surgery + chemoradiation (ECF)
MRC-ST03 [29]	United Kingdom	1100	Stage Ib–IV M0	ECX + surgery + ECX vs ECX/bevacizumab + surgery + ECX/bevacizumab + bevacizumab
CRITICS [30]	The Netherlands	788	Stage Ib–IVa M0	ECC + surgery + ECC vs ECC + surgery + chemoradiation (RT + capecitabine/cisplatin)
CLASSIC [31]	Korea	1024	Stage II, III	Surgery vs surgery + capecitabine/oxaliplatin
SMC IRB [33]	Korea	490	Stage Ib–IV M0	Surgery + capecitabine/cisplatin vs surgery + chemoradiation (RT + capecitabine/cisplatin)
SAMIT [34•]	Japan	1480	T3–4, N0–2	Surgery + UFT vs surgery + S-1 vs surgery + paclitaxel + UFT vs surgery + paclitaxel + S-1
JCOG 501 [36]	Japan	316	Linitis plastica/large ulcerative tumor	Surgery + S-1 vs S-1/cisplatin + surgery + S-1

The ECC and ECX regimens comprise the same chemotherapy elements; however, because different trials use these agents in different doses or timings, the abbreviations have been set to match the original expressions used in the respective citation and/or trial registration.
5-FU—fluorouracil; ECC/ECX—epirubicin, cisplatin, capecitabine; ECF—epirubicin, cisplatin, 5-FU; RT—radiation therapy; UFT—tegafur–uracil.

Studies in Europe

The results of a French neoadjuvant randomized controlled trial were presented at the American Society of Clinical Oncology meeting in 2007 [26]. A total of 224 patients with adenocarcinoma of the lower esophagus (11%), esophagogastric junction (64%), or stomach (25%) were enrolled between 1995 and 2003. The chemotherapy group received two to three courses of 5-FU/cisplatin before surgery, whereas the surgery group immediately proceeded to surgery without additional chemotherapy. The responders of the neoadjuvant group also received postoperative chemotherapy. The 5-year overall survival rate was 38% in the chemotherapy group and 24% in the surgery group (HR 0.69; $P = 0.02$). Although the publication of the details is awaited, this can be considered supportive evidence for the MAGIC trial.

The ECF regimen is now undergoing modifications, as the UK National Cancer Research Institute REAL-2 study for advanced disease showed noninferiority of oral capecitabine to infusional 5-FU [27]. In the "MAGIC-B" trial (MRC-ST03), the 5-FU component of ECF is substituted by capecitabine (ECX). The perioperative ECX is to be compared with ECX plus bevacizumab in a phase 3 setting [28•,29].

Adjuvant chemoradiation is also being tested in Europe. In the Dutch CRITICS trial, patients with resectable gastric cancer receive neoadjuvant ECC and surgery, and then either adjuvant ECC or adjuvant 45-Gy radiation with cisplatin and capecitabine [30].

Studies in East Asia

In Korea, where D2 gastrectomy is routinely performed as in Japan, an adjuvant randomized controlled trial is currently evaluating capecitabine/oxaliplatin after curative surgery for stage II and III gastric cancer (CLASSIC trial) [31]. This is an international study involving institutions in China and Taiwan, and would be the last large-scale randomized controlled trial with a control arm of surgery alone (as further discussed in the Future Perspectives section). Adjuvant chemoradiotherapy is being evaluated in the Samsung Medical Center (Seoul, South Korea) a mega-volume center for gastric cancer surgery (1000 gastrectomies/year). The center published a nonrandomized study using the same regimen as the INT 0116 trial, and results suggested the survival benefit of this regimen even after D2 gastrectomy [32•]. Currently, a randomized controlled trial in a single-institutional setting is under way at the Samsung Medical Center to compare D2 gastrectomy plus adjuvant capecitabine/cisplatin with D2 plus chemoradiation [33].

Following the ACTS-GC trial, adjuvant S-1 has become a standard treatment in Japan, and various trials are active or being planned with S-1 as the reference arm. An adjuvant study (SAMIT) is evaluating the sequential use of paclitaxel and S-1 or oral UFT (tegafur–uracil) for T3/T4 gastric cancer in a 2 × 2 factorial design, expecting that adding paclitaxel to a fluoropyrimidine may reduce peritoneal recurrence [34•]. Following the SPIRITS trial, in which the superiority of S-1/cisplatin to S-1 alone was proven for advanced gastric cancer [35], a phase 2 trial is under way to confirm the feasibility of adjuvant S-1/cisplatin after D2 curative gastrectomy for stage III gastric cancer.

Neoadjuvant chemotherapy has also been evaluated in phase 2 settings. The Japan Clinical Oncology Group (JCOG) completed four trials recruiting high-risk gastric cancer patients (ie, linitis plastica, large diffuse ulcerative tumors, or tumors with bulky nodal metastasis). Three regimens were used: S-1 alone, cisplatin/irinotecan, and S-1/cisplatin. A high pathological response rate with low toxicity was observed with S-1/cisplatin, and a phase 3

trial (JCOG 0501) has started to compare immediate D2 gastrectomy plus adjuvant S-1 with neoadjuvant S-1/cisplatin followed by D2 gastrectomy plus adjuvant S-1 [36].

Future Perspectives

Although the treatment modalities and populations studied were all different, the three trials clearly showed a survival benefit of adjuvant or perioperative therapy for gastric cancer. With the exception of the Korean CLASSIC trial, a control arm of surgery alone has already disappeared in recently launched randomized controlled trials [31]. Large-scale trials will be conducted to compare various combinations of chemotherapy and radiotherapy before and/or after surgery, possibly including new molecular targeting agents.

In the West, the American principle of adjuvant chemoradiation and European principle of perioperative chemotherapy will certainly merge in the near future through cooperative randomized controlled trials. The Dutch CRITICS trial is such an example [30]. International cooperation may become mandatory in the West because of the relatively low incidence of gastric cancers, especially those that are localized.

The increasing trend of esophageal adenocarcinoma and esophagogastric junction tumors in the West are also expected to change the target population. In the middle of the trial, MAGIC extended its inclusion criteria to include esophageal cancer. Currently, there are several phase 2 studies that recruit patients with only esophageal and junctional adenocarcinomas. Application of the results of these trials to stomach cancer merits attention.

In Eastern Asia, the evolution of adjuvant therapy is also awaited, but from a different standpoint. In the INT 0116 and MAGIC trials, the 5-year overall survival rates of the surgery groups are less than 30%, even after curative resection. For a population with such a poor prognosis, toxic combination therapy is warranted even despite the possibility of treatment-related death. However, for a population in which a majority survives by surgery alone, physicians may hesitate about the blind use of highly toxic therapy for all patients, especially before surgery. These physicians would likely prefer primary D2 gastrectomy, careful pathological staging, and selection of high-risk tumors for adjuvant therapy. Simple regimens with high compliance and low toxicity are desirable, and in this regard, oral S-1 monotherapy is acceptable.

According to the Japanese Gastric Cancer Association's nationwide registry of gastric cancer, the 5-year overall survival rate of resected stage IIIb and IV tumors (International Union Against Cancer's TNM [tumor, node, metastasis] staging) was 30.5% and 9.9%, respectively; for resected linitis plastica tumors, it was 16.2% [37•]. Together, these populations would have a comparable prognosis to those of the INT 0116/MAGIC trials, and will likely become a target of toxic combination therapy before and/or after surgery. The JCOG 0501 is such an example [36]. Thus, (neo)adjuvant regimens in Japan and Korea will probably evolve depending on tumor stages, based on the premise that D2 gastrectomy provides sufficient local tumor control and accurate staging.

Conclusions

As a result of three pivotal trials, adjuvant and neoadjuvant therapies for gastric cancer have entered a new era. Large-scale, randomized controlled trials should further produce evidence of benefits from various combination regimens. The East and the West have different patient populations and surgical approaches with different baseline survival rates; therefore, despite some cross-over, their studies are likely to move forward in separate directions. Research on molecular prognostic/predictive markers may be helpful in bridging the gap.

Clinical Trials Acronyms

ACTS-GC—Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer; CALGB—Cancer and Leukemia Group B; CLASSIC—Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer; CRITICS—Chemoradiotherapy after Induction Chemotherapy in Cancer of the Stomach; INT—Intergroup; JCOG—Japanese Clinical Oncology Group; MAGIC—Medical Research Council Adjuvant Gastric Infusional Chemotherapy; MRC-ST—Medical Research Council Study; REAL—Revised European American Lymphoma Classification; RTOG—Radiation Therapy Oncology Group; SAMIT—Stomach Cancer Adjuvant Multi-institutional Trial; SMC IRB—Samsung Medical Center Institutional Review Board; SPIRITS—S-1 Plus Cisplatin vs S-1 in RCT in the Treatment of Stomach Cancer; SWOG—Southwest Oncology Group.

Disclosure

No potential conflict of interest relevant to this article was reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Earle CC, Maroun JA: Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomized trials. *Eur J Cancer* 1999, 35:1059–1064.
2. Mari E, Floriani I, Tinassi A, et al.: Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomized trials. *Ann Oncol* 2000, 11:837–843.

3. Macdonald JS, Smalley SR, Benedetti J, et al.: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001, 345:725–730.

4.•• Cunningham D, Allum WH, Stenning SP, et al.: Perioperative chemotherapy versus surgery alone for respectable gastroesophageal cancer. *N Engl J Med* 2006, 355:11–20.

This large-scale, randomized controlled trial proved the survival benefit of neoadjuvant plus adjuvant chemotherapy for the first time.

5.•• Sakuramoto S, Sasako M, Yamaguchi T, et al.: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007, 357:1810–1820.

The survival benefit of single-agent adjuvant chemotherapy after D2 gastrectomy was proven for the first time in this large-scale, randomized controlled trial.

6. Maehara Y: S-1 in gastric cancer: comprehensive review. *Gastric Cancer* 2003, 6(Suppl 1):2–8.

7. Sakata Y, Ohtsu A, Horikoshi N, et al.: Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1M tegafur-0.4M gimestat-1M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 1998, 34:1715–1720.

8. Kinoshita T, Nashimoto A, Yamamura Y, et al.: Feasibility study of adjuvant chemotherapy with S-1 (TS-1; tegafur, gimeracil, oteracil potassium) for gastric cancer. *Gastric Cancer* 2004, 7:104–109.

9. Siewert JR, Bottcher K, Stein HJ, et al.: Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. *Ann Surg* 1998, 228:449–461.

10. Kim JP, Lee JH, Kim SJ, et al.: Clinicopathologic characteristics and prognostic factors in 10,783 patients with gastric cancer. *Gastric Cancer* 1998, 1:125–133.

11.• Ajani JA, Winter K, Okawara GS, et al.: Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. *J Clin Oncol* 2006, 24:3953–3958.

In this study, preoperative chemoradiation for localized gastric cancer showed a high response rate, including 20% pathologic complete response.

12. Sasako M, Sano T, Katai H, Maruyama K: Radical surgery. In *Gastric Cancer.* Edited by Sugimura T, Sasako M. New York: Oxford University Press Inc.; 1997:223–248.

13.• Kodera Y, Nakanishi H, Ito S, et al.: Prognostic significance of intraperitoneal cancer cells in gastric carcinoma: analysis of real time reverse transcriptase-polymerase chain reaction after 5 years of follow up. *J Am Coll Surg* 2006, 202:231–236.

In this study, the prognostic significance of free cancer cells in the peritoneal wash was shown using a new technique with high sensitivity.

14. Japanese Gastric Cancer Association: Japanese Classification of Gastric Carcinoma: 2nd English edition. *Gastric Cancer* 1998, 1:10–24.

15. Powell J, McConkey CC: Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. *Br J Cancer* 1990, 62:440–443.

16. Blot WJ, Devesa SS, Kneller RW, et al.: Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991, 265:1287–1289.

17. Pinto-De-Sousa J, David L, Seixas M, et al.: Clinicopathologic profiles and prognosis of gastric carcinoma from the cardia, fundus/body and antrum. *Dig Surg* 2001, 18:102–110.

18. Hundahl SA, Macdonald JS, Benedetti J, Fitzsimmons T; Southwest Oncology Group and the Gastric Intergroup: Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. *Ann Surg Oncol* 2002, 9:278–286.

19. Macdonald JS, Smalley S, Benedetti J, et al.: Postoperative combined radiation and chemotherapy improves disease-free survival (DFS) and overall survival (OS) in resected adenocarcinoma of the stomach and gastroesophageal junction: Update of the results of Intergroup Study INT-0116 (SWOG 9008) [abstract 6]. *Presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium;* January 22–24, 2004; San Francisco, CA.

20. Bonenkamp JJ, Songun I, Hermans J, et al.: Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995, 345:745–748.

21. Cuschieri A, Fayers P, Fielding J, et al.: Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. *Lancet* 1996, 347:995–999.

22. Cunningham D, Chua YJ: East meets West in the treatment of gastric cancer. *N Engl J Med* 2007, 357:1863–1865.

23. Jiang Y, Montero AJ, Staveley-O'Carroll KF: Adjuvant and preoperative therapy for localized gastric cancer. *Gastrointest Cancer Res* 2007, 1:139–145.

24. Chemotherapy and radiation therapy after surgery in treating patients with stomach or esophageal cancer. Clinicaltrials.gov. Available at http://clinicaltrials.gov/ct/show/NCT00052910. Accessed February 7, 2008.

25. Oxaliplatin, capecitabine, and radiation therapy in treating patients with stomach cancer that can be removed by surgery. Clinicaltrials.gov. Available at http://clinicaltrials.gov/ct/show/NCT00335959. Accessed February 7, 2008.

26. Boige V, Pignon J, Saint-Aubert B, et al.: Final results of a randomized trial comparing preoperative 5-fluorouracil/cisplatin to surgery alone in adenocarcinoma of stomach and lower esophagus: FNLCC ACCORD07-FFCD 9703 trial [ASCO abstract 4510]. *J Clin Oncol* 2007, 25(18S):4510.

27. Cunningham D, Rao S, Starling N, et al.: Randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer: The REAL 2 trial [ASCO abstract LBA4017]. *J Clin Oncol* 2006, 24(18S):LBA4017.

28.• Starling N, Cunningham D: The role of systemic therapy for localized gastric cancer. *Ann Oncol* 2006, 17(Suppl 10):115–121.

In this article, preoperative and postoperative chemotherapy for localized gastric cancer are reviewed and future perspectives are discussed.

29. Combination chemotherapy with or without bevacizumab in treating patients with previously untreated stomach cancer or gastroesophageal junction cancer that can be removed by surgery. Clinicaltrials.gov. Available at http://clinicaltrials.gov/ct/show/NCT00450203. Accessed February 7, 2008.

30. Randomized phase III trial of adjuvant chemotherapy or chemoradiotherapy in resectable gastric cancer (CRITICS). Clinicaltrials.gov. Available at http://clinicaltrials.gov/show/NCT00407186. Accessed February 7, 2008.

31. CLASSIC – capecitabine and oxaliplatin adjuvant study in stomach cancer. Clinicaltrials.gov. Available at http://clinicaltrials.gov/show/NCT00411229. Accessed February 7, 2008.

32.• Kim S, Lim DH, Lee J, et al.: An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. *Int J Rad Oncol Biol Phys* 2005, 63:1279–1285.

This nonrandomized prospective study suggested a benefit of adjuvant chemoradiation after D2 gastrectomy.

33. Phase III randomized trial of adjuvant XP chemotherapy and XP/RX for resected gastric adenocarcinoma. Clinicaltrials.gov. Available at http://clinicaltrials.gov/show/NCT00323830. Accessed February 7, 2008.

34.• Tsuburaya A, Sakamoto J, Morita S, et al.: A randomized phase III trial of post-operative adjuvant oral fluoropyrimidine versus sequential paclitaxel/oral fluoropyrimidine; and UFT versus S1 for T3/T4 gastric carcinoma: The stomach cancer adjuvant multi-institutional trial group (SAMIT) trial. *Jpn J Clin Oncol* 2005, 35:672–675.

The protocol digest of an ongoing, large-scale, adjuvant randomized controlled trial is shown in this study.

35. Narahara H, Koizumi W, Hara A, et al.: Randomized phase III study of S-1 alone versus S-1 + cisplatin in the treatment for advanced gastric cancer (The SPIRITS trial) [ASCO abstract 4514]. *J Clin Oncol* 2007, 25(18S):4514.

36. Phase III trial of neoadjuvant TS-1 and CDDP for type 4 and large type 3 gastric cancer: JCOG0501. Clinicaltrials.gov. Available at http://clinicaltrials.gov/show/NCT00252161. Accessed February 7, 2008.

37.• Japanese Gastric Cancer Association Registration Committee; Maruyama K, Kaminishi M, Hayashi K, et al.: Gastric cancer treated in 1991 in Japan: data analysis of nationwide registry. *Gastric Cancer* 2006, 9:51–66.

The follow-up data of 7935 gastric cancer patients treated in Japanese leading hospitals were analyzed. This is useful as a reference database of the disease.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 31, 2008 VOL. 359 NO. 5

D2 Lymphadenectomy Alone or with Para-aortic Nodal Dissection for Gastric Cancer

Mitsuru Sasako, M.D., Takeshi Sano, M.D., Seiichiro Yamamoto, Ph.D., Yukinori Kurokawa, M.D., Atsushi Nashimoto, M.D., Akira Kurita, M.D., Masahiro Hiratsuka, M.D., Toshimasa Tsujinaka, M.D., Taira Kinoshita, M.D., Kuniyoshi Arai, M.D., Yoshitaka Yamamura, M.D., and Kunio Okajima, M.D., for the Japan Clinical Oncology Group

ABSTRACT

BACKGROUND

Gastrectomy with D2 lymphadenectomy is the standard treatment for curable gastric cancer in eastern Asia. Whether the addition of para-aortic nodal dissection (PAND) to D2 lymphadenectomy for stage T2, T3, or T4 tumors improves survival is controversial. We conducted a randomized, controlled trial at 24 hospitals in Japan to compare D2 lymphadenectomy alone with D2 lymphadenectomy plus PAND in patients undergoing gastrectomy for curable gastric cancer.

METHODS

Between July 1995 and April 2001, 523 patients with curable stage T2b, T3, or T4 gastric cancer were randomly assigned during surgery to D2 lymphadenectomy alone (263 patients) or to D2 lymphadenectomy plus PAND (260 patients). We did not permit any adjuvant therapy before the recurrence of cancer. The primary end point was overall survival.

RESULTS

The rates of surgery-related complications among patients assigned to D2 lymphadenectomy alone and those assigned to D2 lymphadenectomy plus PAND were 20.9% and 28.1%, respectively (P=0.07). There were no significant differences between the two groups in the frequencies of anastomotic leakage, pancreatic fistula, abdominal abscess, pneumonia, or death from any cause within 30 days after surgery (the rate of death was 0.8% in each group). The median operation time was 63 minutes longer and the median blood loss was 230 ml greater in the group assigned to D2 lymphadenectomy plus PAND. The 5-year overall survival rate was 69.2% for the group assigned to D2 lymphadenectomy alone and 70.3% for the group assigned to D2 lymphadenectomy plus PAND; the hazard ratio for death was 1.03 (95% confidence interval [CI], 0.77 to 1.37; P=0.85). There were no significant differences in recurrence-free survival between the two groups; the hazard ratio for recurrence was 1.08 (95% CI, 0.83 to 1.42; P=0.56).

CONCLUSIONS

As compared with D2 lymphadenectomy alone, treatment with D2 lymphadenectomy plus PAND does not improve the survival rate in curable gastric cancer. (ClinicalTrials.gov number, NCT00149279.)

From the Gastric Surgery Division, National Cancer Center Hospital, Tokyo (M.S., T.S.); the Japan Clinical Oncology Group Data Center, National Cancer Center, Tokyo (S.Y., Y.K.); the Department of Surgery, Niigata Cancer Center Hospital, Niigata (A.N.); the Department of Surgery, National Shikoku Cancer Center, Matsuyama (A.K.); the Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka (M.H.); the Department of Surgery, Osaka National Hospital, Osaka (T.T.); the Department of Surgery, National Cancer Center Hospital East, Kashiwa (T.K.); the Department of Surgery, Tokyo Metropolitan Komagome Hospital, Tokyo (K.A.); the Department of Surgery, Aichi Cancer Center, Nagoya (Y.Y.); and Osaka Medical College, Osaka (K.O.) — all in Japan. Address reprint requests to Dr. Sasako at the Department of Surgery, Hyogo College of Medicine, 1-1, Mukogawa-cho, Nishinomiya, Hyogo, Japan, or at msasako@hyo-med.ac.jp.

N Engl J Med 2008;359:453-62.

GASTRIC CANCER IS THE SECOND LEADING cause of cancer death worldwide, although its incidence is decreasing.[1] About 60% of new cases of gastric cancer occur in eastern Asia; the incidence of new cases in Japan is 100,000 per year. Chemotherapy helps to prolong survival in cases of advanced disease, but surgical resection is the most effective treatment for curable gastric cancer. Reports from the Gastric Cancer Registry and other retrospective studies[2-4] have made radical gastrectomy with extended (D2) removal of regional lymph nodes the standard for the treatment of curable gastric cancer in Japan. Two randomized, controlled European trials that compared the less extended D1 dissection with the D2 procedure failed to show a survival benefit for D2 dissection,[5,6] but lack of experience with the surgical procedure and with postoperative care were thought to account for the poor outcome of patients who underwent D2 lymphadenectomy.[7-9] In 2001, the American Intergroup 0116 study showed that chemoradiotherapy after limited lymphadenectomy (D0 or D1) decreased the local recurrence rate and increased long-term survival,[10] a result suggesting that chemoradiotherapy eliminates the residual lymph-node metastases that could be removed by D2 lymphadenectomy. In 2006, a randomized trial in Taiwan showed a significant benefit in overall survival for a D2 or D3 procedure as compared with D1 dissection, with no increase in operative mortality.[11] These trials indicate that adequate local control is essential for the treatment of gastric cancer. Hence, the standard of care for curable gastric cancer in eastern Asia and the United States is either gastrectomy with D2 lymphadenectomy and without postoperative chemoradiation or D0 or D1 gastrectomy with postoperative chemoradiation.[12-14]

Once the gastric tumor invades the subserosa (stage T2b), the serosa (stage T3), or the adjacent structures (stage T4), metastases can spread to the para-aortic lymph nodes, which are termed N3 nodes according to the *Japanese Classification of Gastric Carcinoma*, second English edition,[15] and M1 nodes according to the International Union Against Cancer (UICC) tumor–node–metastasis (TNM) classification.[16] In advanced gastric cancer, the incidence of microscopic metastases in the para-aortic region is 10 to 30%.[17-19] Because the 5-year overall survival rate of patients with para-aortic nodal metastases can be as high as 20% after systematic dissection,[20] extensive surgery has been performed in Japan since the 1980s for stage T2b, T3, and T4 gastric cancers. However, to our knowledge there has never been a large prospective study to investigate whether para-aortic nodal dissection (PAND) for gastric cancer has a survival benefit. Here we report the final results of a multi-institutional, randomized, controlled trial by the Japan Clinical Oncology Group (JCOG9501) that was conducted to determine whether the addition of systematic PAND to standard gastrectomy with D2 lymphadenectomy improves survival rates among patients with curable gastric cancer. An interim analysis found no differences between the two procedures in the rates of short-term major complications or in-hospital death.[21]

METHODS

ELIGIBILITY

In this trial, we enrolled patients who were younger than 75 years of age and who had histologically proven gastric adenocarcinoma that was considered potentially curable. Additional eligibility criteria, as determined from intraoperative findings, were the presence of a stage T2b, T3, or T4 tumor, the absence of gross metastases to the para-aortic nodes, and negative cytologic findings in peritoneal-lavage fluid. Diagnosis of metastases by examination of frozen sections of para-aortic nodes was not allowed, because sampling of the nodes would involve dissection. The study protocol was approved by the JCOG protocol review committee and the institutional review boards of each of the 24 participating hospitals. In accordance with JCOG policy in 1995 (the year in which enrollment began), all patients gave written informed consent before undergoing randomization.

RANDOMIZATION AND DATA MANAGEMENT

After confirming the eligibility of the patient during surgery, the surgeon contacted the JCOG Data Center by telephone to receive a randomly generated assignment of the patient to standard D2 lymphadenectomy alone or D2 lymphadenectomy plus PAND. Assignments were made by the minimization method according to clinical T stage (T2b vs. T3 or T4), Borrmann macroscopic type (type 0, 1, or 2 vs. type 3 or 5), and institution (patients with Borrmann type 4 tumors were excluded because there was no chance of cure for such patients if they had para-aortic nodal metastases). The surgeon then performed the assigned operation according to the methods described in the protocol.