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Contrast-enhanced sonography of pancreatic carcinoma: correlations with pathological findings

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Editorial on page 666

Background. We examined contrast-enhanced harmonic gray-scale sonographic findings of pancreatic carcinoma in relation to the pathological findings in resected specimens to evaluate correlations between observations made by this modality and the pathological findings. ***Methods.*** The pathological findings of surgical specimens obtained from 16 patients were examined in relation to the contrast-enhanced harmonic gray-scale sonography findings. Lesion vascularity was examined by contrast-enhanced harmonic gray-scale sonography from 20 to 50 s after the injection of Levovist (Schering, Berlin, Germany) (early phase), and lesion enhancement was also monitored at approximately 90 s after injection (delayed phase). ***Results.*** Contrast-enhanced harmonic gray-scale sonography showed positive enhancement in 12 of the 16 lesions (peripheral tumor region alone, $n = 9$; entire tumor, $n = 3$), while the other 4 lesions showed no contrast enhancement in any region. Twelve enhanced regions (9 peripheral tumor region and 3 entire tumor regions) detected by contrast-enhanced harmonic gray-scale sonography showed: (1) mild fibrosis with inflammation, in 10 regions (83%); (2) the presence of both carcinoma cells and residual acinar cells in 8 (67%); and (3) presence of relatively large arteries in 2 (17%). In contrast, 13 non-enhanced regions (4 entire tumor regions and 9 central regions) showed: (1) severe fibrosis in 10 regions (77%); (2) necrosis in 7 (54%); and (3) mucin in 4 (31%). ***Conclusions.*** Contrast-enhanced harmonic gray-scale sonographic findings of pancreatic carcinoma are influenced by interstitial histological features associated with tumor growth.

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Key words: pancreatic carcinoma, contrast-enhanced harmonic gray-scale sonography, helical CT, pathologic findings

Introduction

Pancreatic carcinoma is an aggressive and devastating disease, which is characterized by invasiveness, rapid progression, and profound resistance to treatment.[1] In general, the vascularity of a pancreatic carcinoma lesion is evaluated by helical computed tomography (CT).[2–4] Contrast-enhanced harmonic gray-scale sonography was recently introduced to evaluate the vascularity of pancreatic mass lesions,[5–9] because this modality can visualize blood perfusion in pancreatic mass lesions without motion artifacts,[7] and the technique is simple, easy, and sufficiently noninvasive to be performed on an outpatient basis. It can also be used in patients with renal failure and patients who are allergic to iodine contrast agents. We recently reported that the grade of lesion vascularity on contrast-enhanced harmonic gray-scale sonographic images correlated with the pathological grade of inflammation and correlated inversely with the grade of fibrosis associated with autoimmune pancreatitis.[10] However, there have been no formal studies evaluating any correlations between pathological findings and the findings of contrast-enhanced harmonic gray-scale sonography of pancreatic carcinoma lesions. In the present study, we examined contrast-enhanced harmonic gray-scale sonographic findings in surgically treated pancreatic carcinoma lesions in relation to the pathological findings. We also assessed the enhanced and non-enhanced regions, detected by contrast-enhanced harmonic gray-scale sonography, in relation to the pathological findings.

Subjects and methods

Subjects

Between January 2000 and November 2003, 65 patients with pancreatic carcinoma were admitted to our institutions. Sixteen of the 65 patients were treated surgically, and were the subjects of this study. The patients consisted of 6 men and 10 women, and they ranged in age from 46 to 75 years (mean, 66 years). The maximal diameter (mean ± SD) of the pancreatic mass lesions in the surgical specimens was 37 ± 14 mm. The location of the carcinoma lesion was in the pancreatic head in 12 patients, in the tail in 2, and in both the body and the tail in 2. According to the Japan Pancreas Society (JPS) classification,[11] 1 lesion was stage II, 4 were stage III, 6 were stage IVa, and 5 were stage IVb. Follow-up for all patients ranged from 133 to 1210 days; the follow-up period ended on September 30, 2004. Ten patients died; six patients died of local recurrence, peritonitis carcinomatosa, and liver metastasis; the remaining 4 died of local recurrence and peritonitis carcinomatosa. The survival time ranged from 133 to 511 days. The mean survival time was 308 ± 124 days. Six patients were alive at the end of the study period. Four patients have no recurrence, 1 has lung metastasis, and 1 has local recurrence. The survival time in these 6 patients ranges from 501 to 1180 days. The mean survival time is 925 ± 248 days. All of the patients had been previously examined by conventional and color Doppler sonography. Contrast-enhanced harmonic gray-scale sonography and helical CT examinations were performed in every patient. These two examinations were performed within 1 week of each other. Because no Institutional Review Board existed at the time the study was initiated, the study was performed according to the guidelines of the Helsinki Declaration. Informed consent was obtained from all patients.

Methods

Contrast-enhanced harmonic gray-scale sonography

Contrast-enhanced harmonic gray-scale sonography was performed with a Sonoline Elegra system (Siemens Medical Systems, Issaquah, WA, USA) and a 3.5-MHz convex probe, in all patients, as previously described.[7,10] The pancreas was scanned by native tissue harmonic gray-scale imaging (transmit, 1.6, 1.8, or 2.0 MHz; receive, 3.2, 3.6, or 4.0 MHz Fig. 1A). The pancreatic lesion was then scanned by contrast-enhanced wideband phase-inversion harmonic gray-scale sonography (transmit, 2.5 or 2.8 MHz; receive, 5.0 or 5.6 MHz) at a frame rate of 1 to 5/s, immediately before and after the intravenous injection of a 300-mg/ml concentration of a galactose/palmitic acid mixture contrast agent (Levovist; Schering, Berlin, Germany). Transmission power was 100%, and the mechanical index values were between 1.0 and 1.9. The focus position was just below the bottom of the lesion. Because a certain amount of time is probably required to completely fill pancreatic lesions with the ultrasound contrast agent, especially when extensive fibrosis is present, we decided to evaluate lesion enhancement in two phases (early and delayed) of contrast-enhanced wideband harmonic gray-scale sonography. After the bolus injection of a 7-ml dose of Levovist, at 0.5 ml/s, via a 22-gauge cannula in an antecubital vein, the patients gently inhaled and then held their breath for about 30 s (starting between 20 and 50 s after the contrast medium injection) while the lesion was examined for enhancement (early phase). After observation of the early phase, we froze the image. The images were then reviewed frame-by-frame from cine-loop memories and stored on magneto-optical disks. This procedure took approximately 15–35 s (mean, 25 s) and the time was used to allow pooling of the contrast agent within the pancreatic mass lesion. The entire lesion was then scanned and examined for enhancement about 90 s after injection of the contrast agent, while patients held their breath for a few seconds (delayed phase). The image was frozen again, and the images were then reviewed on a frame-by-frame basis with a cine-loop and stored on a magneto-optical disk for hard copy printing. The entire examination was recorded on S-VHS videotape.

We visually graded tumor enhancement of the pancreatic carcinoma lesions as "no contrast enhancement", "mild enhancement", and "marked enhancement", as compared to the preenhanced appearance on contrast-enhanced wideband phase-inversion harmonic gray-scale sonography.

If the early or delayed phase was the same as the before the finding infusion of Levovist, there was no enhancement (Fig. 2A). "Mild enhancement" was defined as enhancement during the early phase or the delayed phase that was slightly greater than that before the infusion of Levovist (Figs. 1B,C; 2B; 3A,B; 4A,B), and "marked enhancement" was defined as enhancement during the early or delayed phases that was much greater than that before the infusion of Levovist. Mildly and markedly enhanced areas were subdivided into "peripheral region" and "entire tumor". If enhancement was noted in the periphery of the tumor during the early or the delayed phase, it was judged to show peripheral enhancement; if enhancement was seen in the whole tumor during the early or the delayed phase, it was judged to show entire tumor enhancement.

Helical CT

Helical CT was performed with a Proceed SE system (General Electric Medical Systems, Milwaukee, WI,

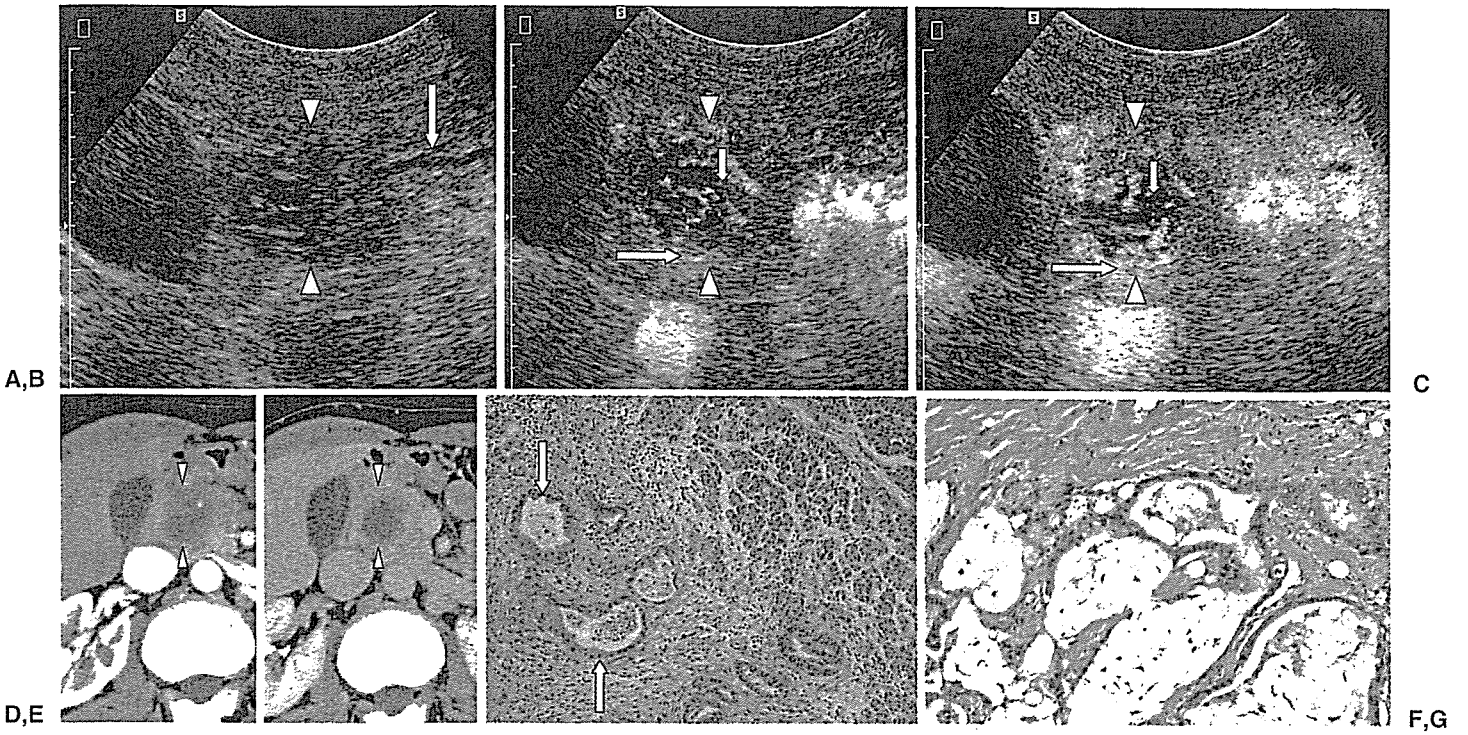

Fig. 1A–G. Findings in a 62-year-old man with mucinous carcinoma in the pancreatic head. **A** Transverse scan pre-enhanced appearance on contrast-enhanced harmonic gray-scale sonogram. *Arrowheads* in **A**, **B**, and **C**, indicate tumor margin. Dilatation of the main pancreatic duct is seen (*arrow*). **B** Early-phase contrast-enhanced harmonic gray-scale sonogram, showing mild enhancement in the peripheral region of the tumor (*long arrow*). *The long* and *short arrows* in **B** and **C** indicate the location from which the histological pictures were taken, corresponding to **F** and **G**, respectively. **C** Delayed phase contrast-enhanced harmonic gray-scale sonogram, showing mild enhancement in the peripheral region of the tumor (*long arrow*). Enhancement of nontumorous parenchyma adjacent to the tumor is seen. **D** Early phase contrast-enhanced computed tomography (CT) scan shows a hypovascular tumor (*arrowheads*). **E** Delayed-phase contrast-enhanced CT scan, showing a mostly hypovascular tumor with isovascularity in a small peripheral region of the tumor; note difference from tumor shown in **D** (*arrowheads*). **F** Surgically obtained histological specimen from the peripheral region of the tumor, corresponding to the enhanced region on both the early and delayed phases of contrast-enhanced harmonic gray-scale sonography, showing the presence of both cancer cells (*arrows*) and residual acinar cells. **G** Surgically obtained histological specimen from the central region of the tumor, corresponding to the non-enhanced region on contrast-enhanced harmonic gray-scale sonography, showing cancer cells, mucin production, and severe fibrosis. **F** H&E, ×100; **G** H&E, ×100

USA) in all patients. A dual-phase study was obtained in each patient, as follows. First, an unenhanced helical sequence through the pancreas and liver was obtained. Next, after the intravenous infusion of 100 ml of iohexol (Omnipaque; Sanofi Winthrop Pharmaceuticals, New York, NY, USA) into an antecubital vein, at a rate of 3 ml/s, an early-phase sequence was obtained after a delay of 25 s, followed by a delayed-phase sequence beginning 80 s after starting the contrast medium infusion. All images were obtained in helical mode, with a 5- or 7-mm collimation and 5- or 7-mm/s table-feed speed. Images were reconstructed at 5- or 7-mm intervals.

We classified the vascularity of pancreatic carcinoma lesions into three grades: "hypovascular", "isovascular", and "hypervascular". Lesions were classified as "hypovascular" if they appeared to be less dense than the surrounding pancreas during the early phase or the delayed phase (Fig. 1D), "isovascular" if they appeared to have the same density as the surrounding pancreas during the early or the delayed phase, and "hypervascular" if they appeared denser than the surrounding pancreas during the early or the delayed phase. Enhanced areas were subclassified into "peripheral region" and "entire tumor". If enhancement was noted in the periphery of the tumor during the early or the delayed phase, it was judged to show peripheral enhancement; if enhancement was noted in the whole tumor during the early or the delayed phase, it was judged to show entire tumor enhancement.

The helical CT findings and the contrast-enhanced harmonic gray-scale sonographic findings were reviewed in a blind fashion. Each image was evaluated by two radiologists and two sonographers, all of whom were unaware of the other study results.

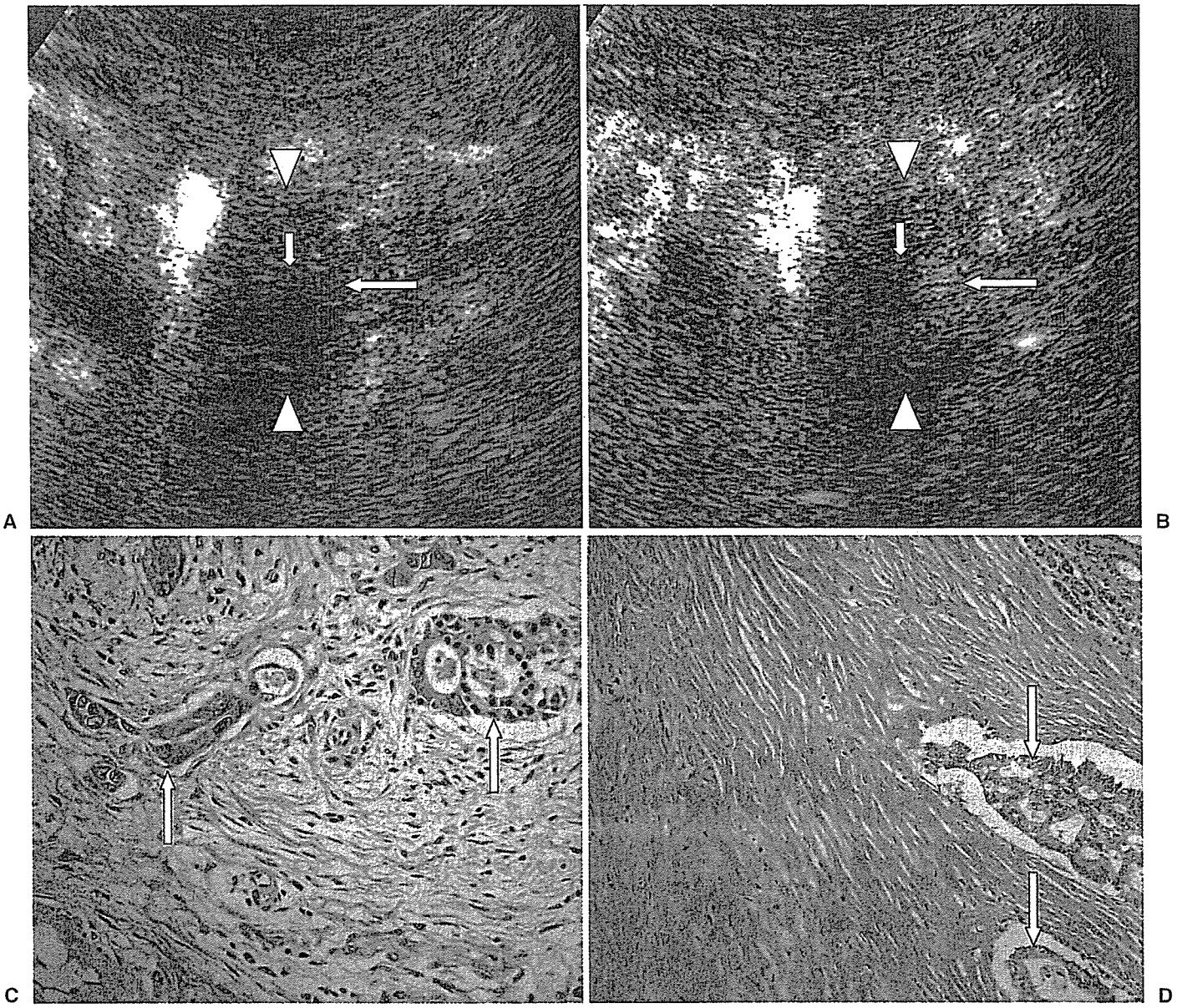

Fig. 2A–D. Findings in a 67-year-old woman with moderately differentiated adenocarcinoma in the pancreatic head. **A** Longitudinal scan early-phase contrast-enhanced harmonic gray-scale sonogram, showing no contrast enhancement in the tumor. *Arrowheads* in **A** and **B** indicate tumor margin. The *long and short arrows* in **A** and **B** indicate the location from which the histological pictures were taken, corresponding to **C** and **D**, respectively. **B** Delayed-phase contrast-enhanced harmonic gray-scale sonogram, showing mild enhancement in the peripheral region of the tumor (*long arrow*). **C** Surgically obtained histological specimen from the peripheral region of the tumor, corresponding to the enhanced region on delayed-phase contrast-enhanced harmonic gray-scale sonography, showing mild interstitial fibrosis with inflammation surrounding cancer cells (*arrows*). **D** Surgically obtained histological specimen from the central region of the tumor, corresponding to the non-enhanced region on contrast-enhanced harmonic gray-scale sonography, showing severe fibrosis and cancer cells (*arrows*). **C** H&E, ×200; **D** H&E, ×200

Pathological findings

The resected specimens were immediately fixed in 10% buffered formalin, serially cut into 4-mm-thick sections, processed routinely, and embedded in paraffin. The paraffin sections were cut into 4-μm-thick sections and were stained with hematoxylin and eosin. Two pathologists, unaware of the results of contrast-enhanced gray-scale sonography or helical CT, interpreted the pathological findings in conference. The lesions were evaluated for the presence or absence of mild fibrosis with inflammation, severe fibrosis, necrosis, mucin, the presence of both carcinoma cells and residual acinar cells in the same lesion, and the presence of relatively large arteries exceeding 500 μm in diameter. Fibrosis of

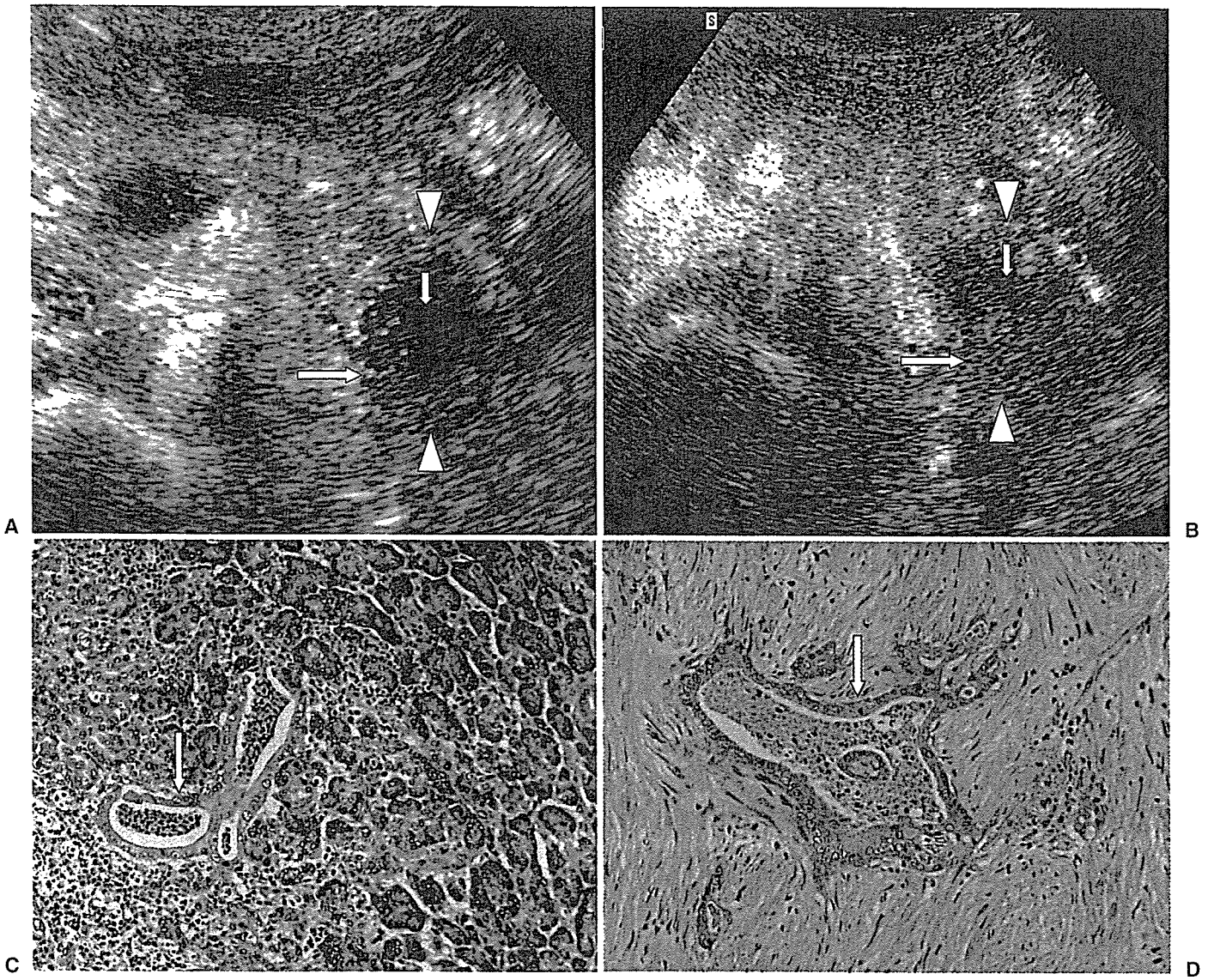

Fig. 3A–D. Findings in a 55-year-old woman with well-differentiated adenocarcinoma in the pancreatic tail. **A** Transverse scan early-phase contrast-enhanced harmonic gray-scale sonogram, showing mild enhancement in a small peripheral region of the tumor (*long arrow*). The *long* and *short arrows* in **A** and **B** indicate the location from which the histological pictures were taken, corresponding to **C** and **D**, respectively. *Arrowheads* in **A** and **B** indicate tumor margin. **B** Delayed phase contrast-enhanced harmonic gray-scale sonogram, showing mild enhancement in the peripheral region of the tumor (*long arrow*). Non-tumorous parenchyma adjacent to the tumor is enhanced. **C** Surgically obtained histological specimen from the peripheral region of the tumor, corresponding to the enhanced region on both the early and dealyed phases of contrast-enhanced harmonic gray-scale sonography, showing the presence of both cancer cells (*arrow*) and residual acinar cells. **D** Surgically obtained histological specimen from the central region of the tumor, corresponding to the non-enhanced region on contrast-enhanced harmonic gray-scale sonography, showing severe fibrosis and cancer cells (*arrow*). **C** H&E, ×150; **D** H&E, ×150

the tumor was graded as "severe" or "mild", based on the severity of the fibrotic changes. Sonographic-pathological correlations were assessed on the basis of the detection of tumor enhancement by contrast-enhanced gray-scale sonography.

Statistical analysis

Data values are expressed as means ± SDs. Relationships between categorical variables were analyzed using the χ^2 test. A P value of less than 0.05 was considered to be statistically significant.

Results

Contrast-enhanced harmonic gray-scale sonography

All lesions were initially detected by conventional sonography. Early-phase contrast-enhanced harmonic

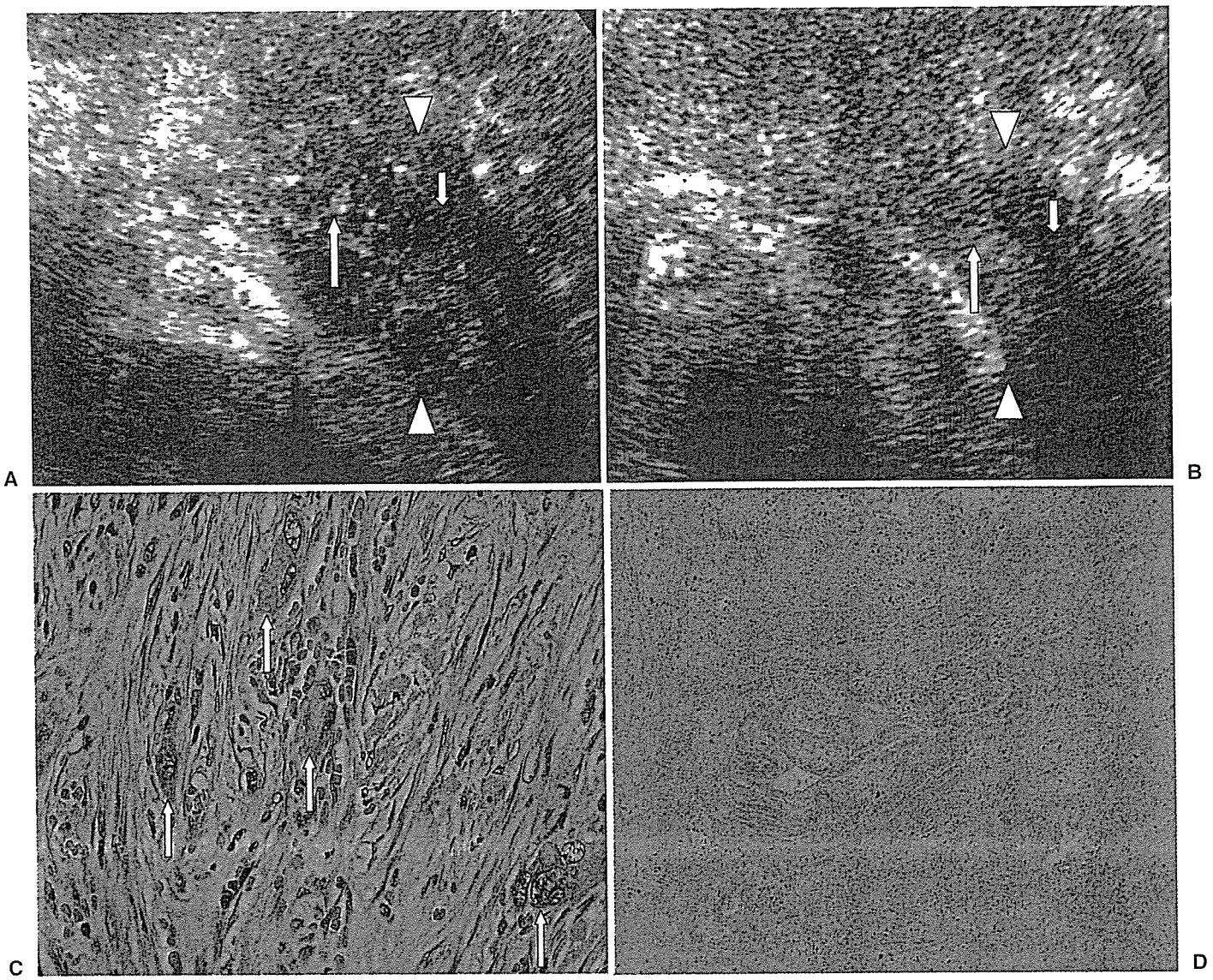

Fig. 4A–D. Findings in a 70-year-old man with poorly differentiated adenocarcinoma extending from the pancreatic body to the tail. **A** Transverse scan early-phase contrast-enahnced harmonic gray-scale sonogram, showing mild enhancement in the peripheral region of the tumor (*long arrow*). *Arrowheads* in **A** and **B** indicate tumor margin. The *long and short arrows* in **A** and **B** indicate the location from which the histological pictures were taken, corresponding to **C** and **D**, respecitvely. **B** Delayed-phase contrast-enhanced harmonic gray-scale sonogram, showing mild enhancement in the peripheral region of the tumor (*long arrow*). **C** Surgically obtained histological specimen obtained from the peripheral region of the tumor, corresponding to the enhanced region on both the early and delayed phases of contrast-enhanced harmonic gray-scale sonography, showing mild interstitial fibrosis with inflammation and an abundance of small vessels surrounding cancer cells (*arrows*). **D** Surgically obtained histological specimen from the central region of the tumor, corresponding to the non-enhanced region on contrast-enhanced harmonic gray-scale sonography, showing necrosis. **C** H&E, ×200; **D** H&E, ×100

gray-scale sonography showed mild enhancement (Figs. 1B, 3A, 4A) in 10 (63%) of the 16 lesions while the other 6 lesions (38%) showed no contrast enhancement. The delayed phase of contrast-enhanced harmonic gray-scale sonography showed mild or marked enhancement (Figs. 1C, 2B, 3B, 4B) in 12 (75%) of the 16 lesions, while the other 4 lesions (25%) showed no contrast enhancement (Table 1).

Helical CT

In the early phase of helical CT, all (100%) pancreatic carcinoma lesions were hypovascular (as in example in Fig. 1D), whereas in the delayed phase, 7 (44%) of the 16 pancreatic carcinomas appeared hypovascular and the other 9 (56%) appeared isovascular in the peripheral region of the tumor (as in example in Fig. 1E; Table 1).

Table 1. Presence or absence of enhancement on contrast-enhanced harmonic gray-scale sonography and helical CT images in patients with pancreatic carcinoma ($n = 16$)

	Contrast-enhanced harmonic gray-scale sonography			Helical CT		
	Marked enhancement	Mild enhancement	No contrast enhancement	Hypervascular	Isovascular	Hypovascular
Early phase	0 (0%)	10 (63%)	6 (38%)	0 (0%)	0 (%)	16 (100%)
Entire tumor	—	3 (19%)	—	—	—	—
Peripheral region	—	7 (44%)	—	—	—	—
Delayed phase	2 (12%)	10 (63%)	4 (25%)	0 (0%)	9 (56%)	7 (44%)
Entire tumor	1 (6%)	2 (12%)	—	—	0 (0%)	—
Peripheral region	1 (6%)	8 (50%)	—	—	9 (56%)	—

Table 2. Correlation between contrast-enhanced harmonic gray-scale sonography and pathological findings or CT findings in patients with pancreatic carcinoma treated surgically ($n = 16$)

Pattern of contrast enhancement/patient no. and histological diagnosis	Pathological findings						
	Severe fibrosis	Necrosis	Mucin	Mild fibrosis with inflammation	Presence of carcinoma and residual acinar cells	Presence of relatively large artery	CT
No contrast enhancement							
1. Well	○	○	—	—	—	—	Negative
2. Moderately	○	○	—	—	—	—	Negative
3. Moderately	○	—	—	—	—	—	Negative
4. Well	○	—	○	—	—	—	Negative
Peripheral enhancement							
5. Moderately[a]	○	○	—	●	—	—	Peripheral
6. Moderately[a]	○	—	○	●	—	—	Peripheral
7. Poorly[b]	—	○	—	●	●	—	Peripheral
8. Poorly[b]	—	○	—	●	●	—	Peripheral
9. Adenosquamous[b]	—	○	—	—	●	—	Peripheral
10. Moderately[b]	○	—	—	—	●	●	Peripheral
11. Well[b]	○	—	○	●	●	—	Peripheral
12. Mucinous[b]	○	—	○	●	●	—	Peripheral
13. Well[b]	○	○	—	●	●	—	Negative
Entire tumor enhancement							
14. Well[b]	—	—	—	●	—	●	Negative
15. Anaplastic[b]	—	—	—	●	—	—	Peripheral
16. Poorly[b]	—	—	—	●	●	—	Negative

Open circles, no contrast-enhanced region; closed circles, enhanced region; well, well-differentiated adenocarcinoma; moderately, moderately differentiated adenocarcinoma; poorly, poorly differentiated adenocarcinoma; adenosquamous, adenosquamous cell carcinoma; mucinous, mucinous carcinoma; anaplastic, anaplastic carcinoma; negative, negative enhancement; peripheral, peripheral enhancement in the delayed phase of helical CT

[a] Delayed phase alone

[b] Both early and delayed phases

Comparison between contrast-enhanced harmonic gray-scale sonographic findings and helical CT findings

The detection rates for positive enhancement of pancreatic carcinoma lesions in the delayed phase of contrast-enhanced gray-scale sonography (75%) and those for isovascular lesions in the delayed phase of helical CT (56%) were not significantly different. Three patients showed hypovascularity in the delayed phase on helical CT; however, these lesions showed positive enhancement in the delayed phase of contrast-enhanced harmonic gray-scale sonography (Table 2). Two of these three patients showed enhancement of the entire tumor and the remaining one showed peripheral enhancement in the delayed phase of contrast-enhanced harmonic gray-scale sonography. However, the detection rate for positive enhancement of pancreatic carcinoma lesions in the early phase of contrast-enhanced gray-scale

sonography (63%) and that for enhancing lesions in the early phase of helical CT (0%) were significantly different, as demonstrated with the χ^2 test ($P < 0.01$).

Correlation between enhanced or non-enhanced regions on contrast-enhanced harmonic gray-scale sonography and pathological findings

In the four pancreatic carcinomas with no contrast enhancement anywhere in the tumor by contrast-enhanced harmonic gray-scale sonography, the regions examined showed severe fibrosis ($n = 4$), necrosis ($n = 2$), and mucin production ($n = 1$). In the nine tumors with mild enhancement in the peripheral region alone, the central regions without contrast corresponded to severe fibrosis ($n = 6$; Figs. 1G, 2D, 3D), necrosis ($n = 5$; Fig. 4D), and mucin production ($n = 3$; Fig. 1G), while the enhanced peripheral tumor regions showed mild fibrosis with inflammation ($n = 7$; Figs. 2C, 4C), the presence of both carcinoma cells and residual acinar cells ($n = 7$; Figs. 1F, 3C), and the presence of a relatively large artery ($n = 1$). In three tumors with enhancement of the entire tumor, the regions examined showed mild fibrosis with inflammation ($n = 3$), the presence of both carcinoma cells and residual acinar cells ($n = 1$), and the presence of a relatively large artery ($n = 1$; Table 2). Therefore, 12 enhanced regions (9 peripheral regions and 3 regions encompassing the entire tumor) detected by contrast-enhanced harmonic gray-scale sonography showed mild fibrosis with inflammation, in 10 regions (83%); the presence of both carcinoma cells and residual acinar cells, in 8 (67%); and the presence of relatively large arteries, in 2 (17%). In contrast, 13 non-enhanced regions (4 entire-tumor regions and 9 central regions) showed severe fibrosis, in 10 regions (77%); necrosis, in 7 (54%); and mucin, in 4 (31%).

Correlation between contrast-enhanced harmonic gray-scale sonographic findings and pathological findings in patients with enhanced peripheral region on contrast-enhanced harmonic gray-scale sonography

All seven (100%) tumors with mild enhancement only in the peripheral region in both the early and the delayed phase of contrast-enhanced harmonic gray-scale sonography showed the combined presence of carcinoma cells and residual acinar cells, five (71%) had mild fibrosis with inflammation and one (14%) had a relatively large artery. By contrast, both (100%) tumors with mild enhancement limited to the peripheral region only in the delayed phase of contrast-enhanced harmonic gray-scale sonography showed mild fibrosis with inflammation.

Correlation between contrast-enhanced harmonic gray-scale sonography findings and histological differentiation

The detection rates for positive enhancement in well- ($n = 5$) or moderately differentiated adenocarcinoma ($n = 5$) was 60%, whereas in poorly differentiated adenocarcinoma ($n = 3$) and other histological lesions ($n = 3$), the rate was 100%.

Correlation between helical CT and pathological findings in operated patients with pancreatic carcinoma

In both the early and the delayed phase of helical CT, seven pancreatic carcinoma lesions were hypovascular as compared to the non-cancerous parenchyma. Five (71%) of these seven non-enhanced regions showed severe fibrosis, three (43%) showed necrosis, and one (14%) showed mucin production. In only the delayed phase of helical CT, nine pancreatic carcinomas appeared isovascular in the peripheral regions of the tumors. Seven (78%) of these nine enhanced regions showed mild fibrosis with inflammation, seven (78%) showed coexistence of carcinoma cells and residual acinar cells, and one (11%) showed the existence of a relatively large artery.

Discussion

In the present study, we examined the contrast-enhanced harmonic gray-scale sonographic findings of pancreatic carcinoma in relation to the pathological findings of resected specimens. Enhanced regions on contrast-enhanced harmonic gray-scale sonography corresponded to mild fibrosis with inflammation or the presence of both pancreatic carcinoma cells and residual acinar cells in the same lesion, whereas non-enhanced regions corresponded to areas of severe fibrosis, necrosis, or mucin.

Pancreatic carcinoma appears most often as a hypovascular mass in the early phase of contrast-enhanced CT.[2–4, 12,13] Presumably, the blood supply to tumors is generally different from that to the normal pancreas, and the difference accounts for the relative tumor hypoattenuation.[14] The rates of isovascular tumor appearance in the early phase of contrast-enhanced CT have been approximately 4%–5% in previous studies.[3, 13] In the present study, we found that 64% of pancreatic carcinoma lesions exhibited some positive enhancement during the early phase of contrast-enhanced harmonic gray-scale sonography, whereas all lesions showed hypovascularity in the early phase on helical CT. During the delayed phase, three lesions showed hypovascularity on helical CT; however,

these lesions showed positive enhancement on contrast-enhanced harmonic gray-scale sonography. Contrast-enhanced harmonic gray-scale sonography is a sensitive modality to evaluate vascular-rich areas of pancreatic carcinoma, and this modality is superior to helical CT in indicating slightly enhanced areas of pancreatic carcinoma lesions more obviously.

As possible explanations for the differences between the results of these imaging techniques; first, the ultrasound contrast agent may remain within the blood vessels, whereas the CT contrast agent is distributed throughout the tissues,[15] i.e., the kinetics of the passage of CT and ultrasound contrast agents are different. Second, we compared the pre-enhancement state and the presence or absence of positive enhancement of the tumor itself during the early and delayed phases of contrast-enhanced gray-scale sonography, whereas we compared the vascularity of pancreatic carcinoma lesions with that of the surrounding pancreas in the early and delayed phases of helical CT images.[7,10] Third, contrast-enhanced harmonic gray-scale sonography permits repeated observations of the same plane, enabling tumor enhancement to be visualized more clearly. This modality detects flow motion as well as bubble disruption, by deliberately adjusting the interval between the transmit pulses.[16]

Demachi et al.[3] reported that the appearance of pancreatic carcinoma on contrast-enhanced CT scans was influenced by the histological features associated with tumor cells. Hypovascular areas in both the early and the late phases of contrast-enhanced CT corresponded to mucin and / or necrosis within the tumor histologically; hypovascular areas in the early phase and iso- or hypervascular areas in the late phase corresponded to dense fibrosis within the tumor; and isovascular areas in both the early and late phases corresponded to increased tumor cellularity and loose interstitial fibrosis or the combined presence of acinar tissue and tumor cells within the tumor.[3] Based on the results from our surgical patients, seven lesions with mild enhancement in the peripheral region of the tumor in both the early and delayed phases of contrast-enhanced harmonic gray-scale sonography showed the combined presence of carcinoma cells and residual acinar cells. Residual acinar cells may exhibit positive enhancement in the early phase of contrast-enhanced harmonic gray-scale sonography, as does the normal pancreatic parenchyma. By contrast, two lesions with mild enhancement in the peripheral regions of the tumor only in the delayed phase of contrast-enhanced harmonic gray-scale sonography showed mild fibrosis with inflammation and these lesions had no residual acinar cells. Johnson and Outwater[17] demonstrated that the region with fibrosis showed gradual enhancement on dynamic magnetic resonance (MR) imaging. Contrast-enhanced harmonic gray-scale sonography may also show gradual enhancement of regions with mild fibrosis. The entirely enhanced tumors detected by this modality were attributable to large areas of mild interstitial fibrosis with inflammation or the presence of a large artery within the tumor. Inflammatory change usually requires blood flow, and such inflamed areas are usually highly vascular.[18] Park et al.[19] reported a large feeding artery to possibly be a factor in the positive enhancement of pancreatic carcinoma lesions. Nagase et al.[9] counted the number of vessels within the most viable tumor regions of pancreatic carcinoma lesions and classified each vessel as either patent or occluded. No signficant relationship between the enhancement effects of contrast-enhanced harmonic gray-scale sonography examinations and the total number of vessels was observed. Conversely, a significant correlation was found between the ratio of patent vessels to total vessels and the gray-scale enhancement.[9]

Invasive carcinomas, such as pancreatic adenocarcinoma, do not exist in isolation. Pancreatic adenocarcinoma is composed of infiltrating carcinoma cells surrounded by a predominance of dense fibrous stroma, which, itself, contains proliferating fibroblasts, small endothelial-lining vessels, inflammatory cells, and trapped residual atrophic parechymal components.[20,21] Well-differentiated adenocarcinoma grows in tubular and glandular patterns and produces abundant dense stroma and mucin. In poorly differentiated adenocarcinoma, the glandular pattern is more bizarre, and epithelial anaplasia is prominent, with mucin production and the desmoplastic response being reduced.[22]

Therefore, severe fibrosis and mucin production are observed more frequently in patients with well-differentiated adenocarcinoma than in those with poorly differentiated adenocarcinoma. On the contrary, interstitial inflammation or residual acinar cells may more frequently be observed in patients with poorly differentiated adenocarcinoma than in those with well-differentiated adenocarcinoma. This may explain why the detection rate of positive enhanced regions on contrast-enhanced harmonic gray-scale sonography in patients with poorly differentiated adenocarcinoma was higher than that in the patients with well- or moderately differentiated adenocarcinoma among our 16 patients with pancreatic carcinoma. We consider the contrast-enhanced harmonic gray-scale sonographic appearance of pancreatic carcinoma to mainly be influenced by interstitial histological features, such as inflammation, fibrosis, residual acinar cells, mucin, and necrosis. These histological features may change according to tumor extension.

If contrast-enhanced harmonic gray-scale sonographic images are obtained only during the early phase, peripheral regions with mild interstitial fibrosis

and inflammation may be missed, as demonstrated in this study. Moreover, enhanced regions in the delayed phase are more obvious than those in the early phase. Thus, a three-phase approach is as important with contrast-enhanced gray-scale sonography as it is with helical CT. Observation with the three-phase approach may be useful in detecting mild interstitial fibrosis and inflammation. Thus, contrast-enhanced harmonic gray-scale sonography may be a useful tool for evaluating the vascularity of pancreatic carcinomas, and it has the ability to visualize vascular areas not detected by helical CT.

Angiogenesis has been shown to be associated with the growth of pancreatic carcinoma lesions, according to the evaluation of microvessels within a pancreatic tumor by immunohistochemical analysis with an anti-CD 34 antibody, as an endothelial cell marker.[23] Therefore, it may be useful to observe the tumor vascularity of pancreatic carcinomas during therapy to evaluate therapeutic efficacy. However, dynamic CT or angiography cannot fully evaluate the tumor vascularity of pancreatic carcinoma. On the contrary, contrast-enhanced harmonic gray-scale sonography is highly sensitive in evaluating the tumor vascularity of pancreatic carcinomas, and it may be useful for evaluating therapeutic efficacy after chemotherapy, radiation therapy, or a combination of the two.

In conclusion, contrast-enhanced harmonic gray-scale sonography may allow the assessment of pathological findings of pancreatic carcinoma lesions. Further study with large numbers of lesions may be needed to establish a correlation between the pathological findings and those seen on contrast-enhanced gray scale sonographic images of pancreatic carcinomas.

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CLINICAL INVESTIGATION

TOXICITIES AND EFFECTS OF INVOLVED-FIELD IRRADIATION WITH CONCURRENT CISPLATIN FOR UNRESECTABLE CARCINOMA OF THE PANCREAS

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Purpose: To evaluate local effects and acute toxicities of involved field irradiation with concurrent cisplatin (CDDP) for unresectable pancreatic carcinoma.

Materials and Methods: Thirty-three patients with unresectable pancreatic carcinoma were treated with chemoradiotherapy. Sixteen were Stage IVA; 17 were Stage IVB. The total prescribed dose of radiotherapy was 50 Gy/25 fractions or 50.4 Gy/28 fractions, using a three-dimensionally determined involved-field that included only the primary tumor and clinically enlarged lymph nodes. Twelve patients received a daily i.v. infusion of CDDP; 21 patients received a combination of CDDP and 5-fluorouracil either i.v. or through the proper hepatic artery.

Results: Twenty-seven (82%) patients completed planned chemoradiotherapy. Nausea was the most frequent complaint. No patient experienced Grade 4 toxicities. More than half achieved pain relief. As for the primary site, only 4 patients (12%) achieved a partial response at 4 weeks; however, 3 additional patients attained >50% tumor reduction thereafter. The most frequent site of disease progression was the liver, and only 3 patients developed local progression alone. No regional lymph nodal progression outside the treatment field was seen. Median survival time and survival at 1 year were 7.1 months and 27%, respectively, for the entire group. Difference in overall survival between patients with and without distant metastases was significant ($p = 0.01$).

Conclusions: Involved-field irradiation with concurrent daily CDDP was well tolerated without compromising locoregional effects. © 2005 Elsevier Inc.

Pancreatic carcinoma, Radiation therapy, Involved field, Concurrent chemoradiation, Pain.

INTRODUCTION

The prognosis of patients with carcinoma of the pancreas is dismal, with less than 5% of patients living for 5 years. For patients with limited-stage disease, only complete surgical resection can offer a chance for long-term survival. However, at the time of diagnosis, less than 15% of patients are suitable for curative surgery (1–3). For patients with unresectable lesions, results of the randomized study by the Gastrointestinal Tumor Study Group (GITSG) showed superior survival in patients treated with concurrent external beam radiotherapy and i.v. 5-fluorouracil (5-FU) as compared with RT alone (4). They also demonstrated that chemoradiotherapy was more effective than chemotherapy alone for advanced pancreatic carcinoma (5). Since the publication of those results, chemoradiotherapy has been commonly used as an initial treatment although this is not the case in the adjuvant setting (6). Several chemotherapeutic agents have been evaluated for pancreatic cancer (7–10). However, at present, a standard regimen of concurrent chemoradiation has yet to be established. One recent trend is to use gemcitabine concurrently with radiotherapy. However, severe gastrointestinal toxicities, such as gastric ulcer requiring blood transfusion, were also reported (11–13). Cisplatin (CDDP) is one of the most commonly used chemotherapeutic agents in the combined chemoradiation setting. For head-and-neck carcinoma and non–small-cell lung carcinoma, concurrent chemoradiotherapy with daily CDDP produced a higher response and a longer survival time than radiotherapy alone (14, 15). In addition, daily low-dose administration of CDDP is believed to be less toxic than the bolus 3-weekly regimen, and there are also some theoretical pharmacokinetic advantages (16, 17).

For pancreatic cancer, the clinical target volume (CTV) for locally advanced carcinoma commonly includes not only the primary tumor but also the regional lymph node area, irrespective of the clinical nodal metastasis (18–20).

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Thus, the planning target volume (PTV) of radiotherapy generally includes some portion of the stomach, the duodenum, and the small intestine, which may result in severe gastrointestinal toxicity when chemotherapeutic agents are administered concurrently with radiotherapy. This limits the delivery of a sufficient dose of radiotherapy. In this institution, to decrease toxicities, radiotherapy for unresectable pancreatic carcinoma has been performed with involved-field irradiation using three-dimensional (3D) treatment planning, where only the primary tumor and clinically enlarged lymph nodes were included in the PTV, without using prophylactic nodal irradiation.

In this study, we report the results of combined involved-field irradiation and concurrent daily administration of CDDP for pancreatic cancer. The objectives were to evaluate the acute toxicities of this combination therapy and to estimate the local and regional tumor response. Effects of this combination on symptomatic relief were also examined.

METHODS AND MATERIALS

Patients and tumor characteristics

Between August 1995 and November 2002, 33 patients with unresectable adenocarcinoma of the pancreas were treated with chemoradiotherapy at the Department of Radiology, Chiba University Hospital. Histologic or cytologic confirmation of pancreatic adenocarcinoma was established for all patients. Sixteen patients had locally advanced unresectable tumors. Seventeen patients had liver metastases at the time of initial diagnosis. A tumor was judged to be unresectable if it obstructed or invaded the celiac axis, superior mesenteric artery, or portal vein on radiologic examination. Patient and tumor characteristics are shown in Table 1. There were 25 men and 8 women. The median age was 65 years (range, 41–78 years). Karnofsky performance status was 70% or higher for all (median, 80%). The tumor size ranged from 20–80 mm (median, 40 mm). According to the 1977 Union Internationale Contre le Cancer (UICC) TNM classification, 16 patients were Stage IVA, and the remaining 17 patients were Stage IVB. The most common chief complaint was abdominal pain (23/33), which required daily treatment with analgesics for most patients.

Radiotherapy

All patients received external beam radiotherapy using 10 MV photons. For all patients, treatment planning was performed using a computed tomography (CT) simulator (AcQSIM PQ2000S; Philips Medical System, Andover, MA). Computed tomography images were acquired using a 3-mm slice thickness with free breathing. The dose distribution and dose volume histogram (DVH) were calculated using a 3D treatment planning system (FOCUS; CMS Japan K.K., Tokyo, Japan). The gross target volume (GTV) was the primary tumor and surrounding clinically enlarged lymph nodes that was more than 1.5 cm in diameter identified on CT scan. The CTV was defined as the GTV plus a 0.5 cm margin. The PTV was the CTV plus 1.0–1.5 cm for daily patient set-up variation and respiratory movement. No prophylactic nodal irradiation was given. A fractional daily dose of 1.8–2 Gy (5 days/week) at an isocenter, up to a total dose of 50.0 or 50.4 Gy, was prescribed. The CTV was encompassed within the 95% isodose line.

Table 1. Patient characteristics

Characteristics	Values
Male/female	25/8
Age, range (median)	41–77 (65)
Chief complaint	
Pain	23
Appetite loss	4
Jaundice	2
Diabetes mellitus	2
Other	2
Karnofsky performance status (%), 70/80/90	4/16/13
Tumor location, Head/body/tail	13/11/9
Size of tumor (median)	20–80 mm (40 mm)
Clinical stage, IVA/IVB*	16/17

* 1997 Union Internationale Contre le Cancer, TNM.

Chemotherapy

All patients received chemotherapy with a daily low-dose CDDP concurrently with radiotherapy. Twelve of 16 patients without liver metastases received daily i.v. infusions of CDDP (5 mg/m^2), starting from the first day to the last day of radiotherapy. Thirteen of 17 patients with liver metastases received a combination of CDDP (3 mg/m^2) and 5-FU (300 mg/m^2) through the proper hepatic artery using an implanted reservoir. The remaining 8 patients received a combination of CDDP (5 mg/m^2) and 5-FU (300 mg/m^2) i.v. The CDDP was delivered 1 h before radiotherapy, and the 5-FU was administered by a 24-h continuous infusion, Monday through Saturday. A catheter for intra-arterial drug administration was inserted mainly from the femoral artery. The gastroduodenal artery and right gastric artery were occluded by a steel coil, to avoid inflow of anticancer drugs to other organs. After confirming the presence of the tip of heparin-coated catherter in the proper hepatic artery, reservoir connected to the catherter was implanted in the s.c. pocket in the abdominal wall.

After this combined chemoradiotherapy, treatments for each patient were individualized. Most received 5-FU or its oral derivatives thereafter. Some received systemic chemotherapy using gemcitabine.

In-field tumor response evaluation and statistical methods

Within 4 weeks after chemoradiotherapy, all patients underwent a CT scan and ultrasonography of the abdomen to determine the in-field tumor response. Serum CA19-9 values before and after the treatments were examined for all. As for the local response, a complete response (CR) was defined as a total resolution of the primary tumor. A partial response (PR) was defined as at least a 50% reduction in the product of the 2 diameters of the primary tumor. No change (NC) was defined as <50% reduction and <25% increase in the size of the primary tumor. Disease progression (PD) was defined as an increase of >25% of the size of the primary tumor.

Since pain is the most common symptom of advanced pancreatic carcinoma, the clinical benefit of the treatment was also assessed by measuring pain reduction. Pain intensity was measured weekly on a visual analog scale of 0–10. Analgesic consumption was monitored for each patient. Positive effects for pain reduction were defined as a decrease in analgesic consumption or a decrease in pain grade according to the visual analog scale, without increasing the dose of analgesics. Patients who achieved pain relief by

increasing the dose of analgesics were not included in the responder for pain.

Acute toxicities were graded using the common toxicity criteria of the National Cancer Institute (version 2.0). Survival and in-field progression free time were calculated from the first day of chemoradiotherapy using the Kaplan-Meier actuarial method. Patients who were lost to follow-up with active disease were considered as dead at the last contact date for survival calculation.

RESULTS

Irradiation fields

To reduce the irradiation dose to the gastrointestinal system, a lateral beam was added for 28 patients. Of those, 24 patients were treated with a 3-field or 4-field coplanar beam arrangement (box technique), and 4 were treated with 2 ports using anterior and lateral beams. For the remaining 5 patients, opposed anterior-posterior fields or opposed oblique fields were used to reduce the dose to other major organs, such as the liver or kidney. The field size of the anterior-posterior port ranged from 8 × 8 cm to 12 × 18.5 cm (median, 10 × 10 cm), and that of the lateral port from 8 × 8 cm to 18.5 × 11.5 cm (median, 10 × 9 cm). For 11 patients, a DVH was calculated for the liver and kidney. The liver volume that received >30 Gy ranged from 0–18% (median, 6%). The total kidney volume that received >20 Gy ranged from 3–45% (median, 16%), where both kidneys were considered as a single organ.

Compliance with therapy

Of 33 patients, 30 (91%) received >40 Gy. Twenty-seven (82%) patients completed planned chemoradiotherapy of a total dose of 50 Gy or 50.4 Gy. Of 12 patients who received daily i.v. CDDP (5 mg/m^2), 1 stopped treatment at 43.2 Gy because of Grade 3 leukopenia. Eight patients who received a combination of CDDP (5 mg/m^2) and 5-FU (300 mg/m^2) i.v. injection completed planned chemotherapy. Of the 13 patients who received combination of intra-arterial CDDP (3 mg/m^2) and 5-FU (300 mg/m^2) through the hepatic artery, 5 patients discontinued therapy; rapid progression of disease in 3 (carcinomatous peritonitis at 14 Gy in 1 and deterioration of performance status at 34 Gy and 42 Gy each in 1), reservoir trouble at 38 Gy in 1, and liver abscess at 42 Gy in 1.

Acute toxicities during chemoradiotherapy for all patients are listed in Table 2. Fifteen patients (45%) experienced Grade 2 or greater nausea, which was the most frequently observed complaint within this regimen. Seven patients (21%) had Grade 3 nausea. Three patients (9%) suffered Grade 3 anemia without requiring blood transfusion. Three patients (9%) suffered Grade 3 leukopenia. No patient experienced Grade 4 acute toxicities. There was no significant difference in the toxicity grade between chemotherapy regimens. None of the treatment factors such as dose/fraction of radiotherapy, number of treatment ports, or field size influenced the development of Grade 2 or higher toxicities. No patients developed liver or renal dysfunction attributed to this chemoradiotherapy.

Table 2. Acute toxicities

Toxicity	Toxicity grade*			
	0–1	2	3	4
Leukopenia	19	11	3	0
Anemia	26	4	3	0
Thrombocytopenia	29	4	0	0
Nausea/vomiting	16	9	6	0
Gastric ulcer/duodenal ulcer	29	3	1	0

* National Cancer Institute common toxicity criteria, ver. 2.0.

Response to treatment

Pain relief. At the start of this treatment, 23 patients had abdominal or back pain due to pancreatic carcinoma. Eighteen patients needed analgesics, predominantly morphine hydrochloride (20–120 mg/day; median: 40 mg/day). Changes in the pain grade and needs for daily analgesic consumption at the completion of chemoradiotherapy are shown in Table 3. Of 23 patients with pain before treatment, 12 patients (52%) achieved pain relief with this therapy. Seven patients were stable in pain. The other 4 patients progressed in pain intensity. None of the treatment parameters, such as the regimen of chemotherapy, tumor size, or total dose of radiotherapy, influenced the pain relief.

Local effect and serum CA19-9. At 4 weeks after treatment, as for the primary sites, a PR was obtained in 4, NC in 26, and PD in 3 (Table 4). For 3 patients with NC, the primary tumor showed gradual shrinkage and >50% reduction was obtained at 2 months, 3 months, and 10 months, respectively, after the end of chemoradiotherapy. At the time of data analysis, no obvious tumor could be detected radiographically in 3 patients (initial PR in 2 and NC in 1).

Before the treatment, serum CA19-9 was elevated in 15 of 16 patients without liver metastases. Of those, the value of CA19-9 decreased after chemoradiotherapy in 11 (73%). In 2 of the remaining 4 patients whose level of CA19-9 increased despite treatment, liver metastases were newly diagnosed. For the other 2, disease was stable. Serum CA19-9 was initially elevated in 15 of 17 patients with liver metastasis. Of those, the value of CA19-9 decreased after chemotherapy in only 4 patients (27%). Of 11 patients whose CA19-9 value had increased despite chemoradiotherapy, 9 progressed to liver metastases, and 2 were stable in radiographical evaluation. Of all patients whose CA19-9 value increased, 11 patients (78%) progressed to liver metastases.

Failure pattern. At the end of chemoradiotherapy, 15 patients had disease, progression, 1 for a local site only, 2 for local and metastatic sites, and 12 for a metastatic site only. For the remaining 18 patients who had at least NC in the primary site without metastatic progression at 4 weeks after chemoradiotherapy, the initial failure pattern is summarized in Table 5. Local progression was observed in 2, metastatic progression in 9, and simultaneous local with distant in 1, with a median time to progression of 8.9 months. No patient developed regional lymph nodal pro-

Table 3. Pain relief

	Pain intensity*		
Analgesics consumption	Improved	Stable	Progressed
Decrease	2	3	0
No change	7	7	0
Increase	1	1	2

* Evaluated by the Visual Analogue Scale.

gression outside the PTV. We could not get information for 3 patients, because they were transferred to another hospital. At the time of data analysis, 23 have died of pancreatic carcinoma.

Overall survival is shown in Fig. 1. Median survival time and survival at 1 year were 7.1 months and 27%, respectively, for the entire group; 10.6 months and 44%, respectively for patients without metastases; 3.6 months and 12%, respectively, for patients with metastases, with a median follow-up time of 7.1 month. Difference in overall survival between patients with and without distant metastases was significant (log–rank, $p = 0.01$). Three patients lived more than 2 years after treatment.

DISCUSSION

The CTV for locally advanced pancreatic carcinoma commonly includes the primary tumor with the regional lymph node area, such as the pancreaticoduodenal, porta hepatis, celiac, and suprapancreatic nodes. The size of the anterior-posterior opposed ports usually ranges from 10 × 10 to 14 × 14 cm and even larger (21). Thus, the PTV for pancreatic carcinoma unintentionally includes some portion of the stomach, the duodenum, and the small intestine, which may cause severe gastrointestinal toxicity when chemotherapeutic agents are administered concurrently with radiotherapy. Burris *et al.* (7) indicated that gemcitabine provided an advantage compared with 5-FU with respect to clinical benefit or objective response. Although gemcitabine, which is considered one of the new key drugs for pancreatic carcinoma, is now preferentially used in clinical trials, several investigators reported severe toxicities, such as bleeding from gastric ulcers, requiring blood transfusion (11–13). This limits the delivery of a sufficient dose of chemotherapy or radiotherapy to the pancreatic carcinoma.

Results of many clinical trials have demonstrated that more than half of patients develop distant metastases as the initial disease progression (21–25). McGinn *et al.* (26) demonstrated that 3D-conformal radiotherapy for the primary lesion not including the prophylactic lymph node area could reduced toxicities of concurrent chemoradiotherapy using gemcitabine. They recommended systemic use of gemcitabine concurrently with a relatively lower total dose of 36 Gy. However, there is little information concerning concurrent chemoradiotherapy with involved-field irradiation using a higher total dose by conventional fractionation. In this study, radiotherapy was administered by conventional fractionation up to 50 Gy, which is within tolerable doses of the small intestine (27).

Twenty-eight (82%) of all patients attained planned chemoradiotherapy. And except for 2 patients (1 with rapid progression of the primary site and another with reservoir trouble), 91% of patients completed chemoradiotherapy of more than 40 Gy. As for toxicities, nausea/vomiting was most frequently observed. Gastrointestinal toxicities were common for chemoradiation using CDDP and 5-FU. In our study, about half of all patients experienced Grade 2 or greater nausea/vomiting. However, none discontinued therapy due to these symptoms. No patient developed severe toxicities such as gastrointestinal bleeding. Although, in this study, field size did not influence the development of nausea, the PTV was rather small since the lymph node area was not included in the target volume. Our smaller PTV may have contributed to the relatively lower incidence of gastrointestinal toxicities. No patient experienced Grade 4 hematologic toxicities. These results demonstrate the feasibility of this therapy.

Table 4. In-field tumor response at the end of chemoradiotherapy

Complete response	Partial response	No change	Disease progression
0	4	26	3

Table 5. Patterns of initial disease progression

No evidence of disease	3
Local	2
Distant	
Liver	3
Liver + peritoneum	1
Peritoneum	2
Nonregional lymph node	3
Local + distant (peritoneum)	1
Unknown	3

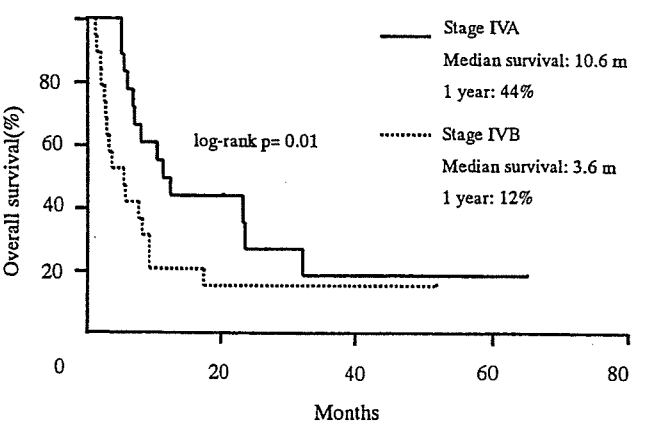

Fig. 1. Overall survival according to clinical stage.

Pain is the most devastating symptom of locally advanced pancreatic carcinoma. Many patients required some kind of analgesic. Morphine hydrochloride is most commonly used; however, pain relief is unsatisfactory for some patients, and requires other interventions, such as neurolytic block (28). Thus, pain relief is one of the most important goals for patients with advanced pancreatic carcinoma. It was reported that radiotherapy is effective in pain relief in 45%–80% of patients (18, 21). In the current study, more than half of the patients who had abdominal or back pain achieved pain relief. Results of the present study demonstrate that involved-field irradiation was also effective for pain relief.

At the end of chemoradiotherapy, only 4 patients (12%) achieved a PR. This response rate was unsatisfactory, as was reported in other studies (28–30). However, 3 patients achieved total resolution of the primary tumor, and another 3 patients achieved >50% reduction during the follow-up period. There were only 3 patients who had local progression alone as the first site of recurrence, and there were 3 patients who lived more than 2 years without local progression. Thus, it was considered that our involved-field irradiation was at least equally effective for local control as those of others using conventional fields. None of the patients who could not achieve local control lived very long. Thus, local control was considered a surrogate for longer survival. Boz *et al.* (21) reported that 23% of their patients achieved a PR using continuous infusion of 5-FU at dose of 300 mg/m^2/day and 59.6 Gy of radiotherapy. It is considered that delivering a higher dose to the primary tumor, using a more localizing field concurrently with chemotherapy, is more effective for local control. It seems that the local response is key to both symptomatic relief and longer survival.

In the present study, the first site of progression was a distant metastasis in 24/27 patients whose disease had eventually progressed. The failure pattern in this study was similar to those of other studies using prophylactic nodal irradiation. No patient progressed within the prophylactic lymph node area outside the PTV. Thus, it was considered that decreasing the PTV using involved-field may not influence patient survival, although this must be confirmed by prospective study.

For patients without distant metastases, the median survival time was 10.6 months, and the overall survival at 1 year was 44%. These are almost same as results of randomized studies (4, 5). For patients who developed distant metastases, the median survival time was 3.6 months, and survival at 1 year was 12%. Most of them failed at the metastatic site. Thus, to improve patient survival, it seems necessary to establish a more intensive systemic chemotherapy regimen. Results of the present study showed that involved-field radiation therapy was well tolerated without compromising locoregional control. Administration of higher doses to the primary tumor using involved-field radiotherapy may be one of the most useful strategies for treating advanced pancreatic carcinoma in the future chemoradiation setting.

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Phase I trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer

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The objective of this study was to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of S-1, an oral fluorouracil derivative, combined with gemcitabine, the current standard treatment for advanced pancreatic cancer (APC). The subjects were histopathologically proven APC patients with distant metastasis. S-1 was administered orally twice daily each day for 14 days and gemcitabine on days 8 and 15 of each cycle, and this was repeated every 21 days. Doses of each drug were planned as follows: level 1: 800/60, level 2a: 800/80, level 2b: 1000/60, level 3: 1000/80 (gemcitabine ($mg\,m^{-2}$)/S-1 ($mg\,m^{-2}\,day^{-1}$)). In all, 21 patients with APC were enrolled. The main grade 3–4 toxicities observed during first cycle were neutropenia (33%), anaemia (10%), thrombocytopenia (14%) and anorexia (10%). There were no DLT observed in level 1. Three of six patients in level 2a had DLT and this level was considered the MTD. In all, 12 patients in level 2b had no DLT and this level was selected as the recommended dose. Applicable responses were one complete response and nine partial responses (48%). As toxicities were well tolerated and antitumour activities seem to be promising, this combination can be recommended for further phase II studies with APC.
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The incidence and mortality of pancreatic cancer has increased so rapidly over the past 20 years in Japan that it is now the fifth leading cause of cancer mortality in the country (Matsuno *et al*, 2004). The 5-year survival rate is still poor, at less than 10%, commonly considered to be linked to the high incidence of distant metastasis even at initial diagnosis, as well as the tumour's resistance to anticancer agents. Innovation in systemic chemotherapy is thus urgently needed to improve the survival of patients with pancreatic cancer (Glimelius *et al*, 1996; Evans *et al*, 1997).

Since 1997, gemcitabine has been the most widely used chemotherapeutic agent in advanced pancreatic cancer (APC) and was reported to have significantly better symptom control in APC compared with 5-FU in a randomised phase III clinical study (Burris *et al*, 1997). Even with gemcitabine, however, monotherapy has obvious limitations in APC and various combinations with other agents have been investigated. The combination of gemcitabine and 5-FU is shown to have a marked synergistic cytotoxic effect against pancreatic cancer cells in *in vitro* assay (Bruckner *et al*, 1998). Phase I and II studies of combined therapy of gemcitabine with 5-FU demonstrated superior results (Berlin *et al*, 1998, 2000; Cascinu *et al*, 1999; Hidalgo *et al*, 1999; Matano *et al*, 2000). However, adding weekly intravenous bolus 5-FU to weekly gemcitabine did not confer a significant survival benefit in a randomised trial (Berlin *et al*, 2002). There are no randomised data on the combination of infusional 5-FU with gemcitabine in APC.

S-1 is a new oral fluorinated pyrimidine developed by Taiho Pharmaceutical Co. Ltd (Tokyo, Japan). The agent contains tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) in a molar ratio of FT:CDHP:Oxo = 1:0.4:1, based on a biochemical modulation of 5-FU (Shirasaka *et al*, 1996a, b). Tegafur, a prodrug of 5-FU, is gradually converted to 5-FU and is rapidly catabolised by dihydropyridine dehydrogenase (DPD) in the liver. 5-Chloro-2,4-dihydroxypyridine is a competitive inhibitor of 5-FU catabolism, being about 180 times more potent than uracil in inhibiting DPD (Tatsumi *et al*, 1987). When tegafur is combined with CDHP, the resulting high 5-FU levels are maintained in both plasma and tumour. In addition, it has been suggested that CDHP has the potential to enhance the antitumour activity of 5-FU against subcutaneous tumour in nude mice, using human pancreas carcinoma cells with a high tumoral DPD activity (Takechi *et al*, 2002). Oxo inhibits the enzyme orotate phosphoribosyltransferase, the major enzyme responsible for 5-FU activation in colon cancer (Peters *et al*, 1991). Oxo preferentially localises in the gut rather than in the tumour and has a potential biochemical effect on the enzyme orotate phosphoribosyltransferase, thereby selectively inhibiting the formation of 5-FU nucleotides in the gut and theoretically reducing gastrointestinal side effects (Takechi *et al*, 1997). In phase II studies for advanced gastric cancer conducted in Japan, S-1 showed high response rates of 44–49% (Sakata *et al*, 1998; Koizumi *et al*, 2000), and the usefulness of S-1 was also reported in head and neck (Inuyama

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et al, 2001), breast (Saeki *et al*, 2004) and colorectal cancer patients (Ohtsu *et al*, 2000). In studies outside Japan, the phase II studies of S-1 against gastric (Chollet *et al*, 2003) and colorectal cancer (Van den Brande *et al*, 2003) in Europe by the EORTC-Early Clinical Study Group revealed moderate activity. The antitumour activity of S-1 in patients with pancreatic cancer has not yet been investigated outside Japan, but preliminary favourable results of S-1 have been reported in Japanese early phase II study of patients with APC (Okada *et al*, 2002).

The administration of oral S-1 is more convenient and simulates the effect of continuous infusion of 5-FU. We anticipated that combination chemotherapy of gemcitabine and S-1 would be effective through the additive and synergistic activity of gemcitabine and 5-FU derived from S-1. As yet, the combination regimen of gemcitabine and S-1 for patients with APC has not been investigated. Therefore, the author performed a phase I study to evaluate the safety of treatment combined gemcitabine with S-1 and to determine the maximum tolerated dose (MTD) of each drug for patients with APC.

PATIENTS AND METHODS

Patient selection

Patients with histopathologically proven APC with distant metastasis were eligible for the study. Other eligibility criteria included: 20–74 years of age, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less (ambulatory and capable of self-care), estimated life expectancy of more than 2 months, adequate renal function (normal serum creatinine and blood urea nitrogen levels), liver function (total bilirubin level $\leqslant$2.5 times upper normal limit (UNL) or $\leqslant$3 times UNL after biliary drainage if the patient had obstructive jaundice and serum transaminases (GOT, GPT) levels $\leqslant$2.5 times UNL or $\leqslant$3 times UNL), bone marrow reserve (white blood cell count between 4000 and 12 000 mm^{-3}, neutrophil count $\geqslant$2000 mm^{-3}, platelet count $\geqslant$100 000 mm^{-3} and haemoglobin level $\geqslant$9.5 g dl^{-1}) and pulmonary function ($PaO_2 \geqslant 70$ mmHg). If the patients had a previous history of cancer treatment, that treatment (tumour resection, chemotherapy, immunotherapy, or radiotherapy) had to have been discontinued for at least 4 weeks before entry into the study. All subjects provided written informed consent.

The exclusion criteria were as follows: pulmonary fibrosis or interstitial pneumonia, marked pleural or pericardial effusion or marked peripheral oedema, severe heart disease, difficult to control diabetes mellitus, active infection, pregnant or lactating females, women of childbearing age unless using effective contraception, severe drug hypersensitivity, metastases to the central nervous system, severe neurological impairment or mental disorder, active concomitant malignancy and other serious medical conditions.

This study was approved by the institutional review board of Chiba University Graduate School of Medicine.

Study design

This was an open-label, single-centre, nonrandomised, dose-escalating phase I study. All laboratory tests required to assess eligibility had to be completed within 7 days prior to the start of treatment. S-1 was administered orally twice daily after a meal for 14 consecutive days (from the evening of day 1 to the morning of day 15), followed by a 1-week break. Each capsule of S-1 contained 20 or 25 mg of tegafur. Individual doses were rounded down to the nearest pill size less than the calculated dose, given the available formulation. Gemcitabine was administered as a 30-min intravenous infusion on days 8 and 15 of each cycle. The cycle was repeated every 21 days. This schedule was based on an *in vitro* study which showed maximum synergy when fluoropyrimidine precedes exposure to gemcitabine (Rauchwerger *et al*, 2000). The dose of each drug in this study was planned as follows: level 1 was S-1 60 mg m^{-2} day^{-1} and gemcitabine 800 mg m^{-2}, level 2a was S-1 80 mg m^{-2} day^{-1} and gemcitabine 800 mg m^{-2}, level 2b was S-1 60 mg m^{-2} day^{-1} and gemcitabine 1000 mg m^{-2}, level 3 was S-1 80 mg m^{-2} day^{-1} and gemcitabine 1000 mg m^{-2}. However, only when neither level 2a nor level 2b reached the MTD would patients be assigned to dose level 3.

Definition of dose-limiting toxicities (DLTs) and MTD

Dose-limiting toxicities (DLTs) were determined during the first treatment cycle. Dose-limiting toxicity was defined, using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) scale (version 2.0), as one or more of the following effects attributable to study drug: (a) grade 3 or 4 neutropenia complicated by fever; (b) grade 4 neutropenia lasting longer than 4 days; (c) grade 4 thrombocytopenia; (d) any other grade 3–4 nonhaematologic toxicity except anorexia, nausea and vomiting in the absence of appropriate antiemetics and (e) delay of recovery from treatment-related toxicity for more than 2 weeks. At least three patients were enrolled at each dose level. If DLT was observed after the first cycle in one or two patients, three additional patients were placed on that dose level. If only one or two of six patients experienced DLT, dose escalation would continue. There was no dose escalation in individual patients. The MTD of the combination was defined as the dose level that produced DLT in $\geqslant$3 of six patients or in all of the initial three patients. The recommended dose (RD) was defined as the dose level that is one level under MTD considering the toxicity and tolerability in outpatient setting.

Pretreatment and follow-up studies

Before entry into the study, all patients gave a full history and underwent a physical examination. A complete blood count (CBC) with differential, electrolyte levels, and creatinine levels were measured. Routine chemistry tests, urinalyses and 24-h urine collections were performed to detect proteinuria. Electrocardiograms, chest X-rays and computed tomographic scans of the chest and abdomen were performed at baseline in all patients. Additional imaging investigations were performed if clinically indicated or for disease measurement. A complete blood count with differential, serum chemistry, creatinine level, and electrolyte level were measured weekly. Computed tomographic scanning and imaging of the measurable disease to assess tumour response were performed every two cycles. At the completion of the study, all clinical, laboratory, radiologic imaging and other evaluations were repeated. After completion of the study, patients underwent follow-up examinations every 2 months until death. Additional treatment after disease progression was left to the discretion of the treating physician.

Assessment of efficacy

All patients were included in efficacy measurements on an intent-to-treat basis. Tumour responses were evaluated according to the World Health Organization's criteria (World Health Organization, 1979). A complete response (CR) was defined as the disappearance of all evidence of cancer for 4 weeks or longer. A partial response (PR) was defined as a 50% or more reduction in the sum of the product of the longest perpendicular dimensions of all lesions for 4 weeks or longer without any evidence of new lesions or the progression of any lesions. Stable disease (SD) was defined as less than a 50% reduction or less than a 25% increase in the sum of the product of the longest perpendicular dimensions of all lesions without any evidence of new lesions. Progressive disease (PD) was

defined as a greater than 25% increase in one or more lesions or the appearance of any new lesion. To assess objective response, patients were evaluated every 6 weeks (two cycles) by three independent radiologists.

Serum CA19-9 levels were measured every 4 weeks during the chemotherapy using a commercially available chemiluminescent enzyme immunoassay based on the two-step sandwich method (CL-EIA). A value of 37 U ml^{-1} was defined as the upper limit of the normal.

Overall survival was estimated from the date of first treatment to death or last follow-up visit, calculated using the Kaplan–Meier method, and confidence intervals (CI) were based on Greenwood's formula.

RESULTS

All 21 patients with APC registered between January 2003 and March 2004 had primary sites. Out of 21, 18 patients had liver metastasis except one who had lung metastasis, and two who presented with peritoneal carcinomatosis only (Table 1). Although the eligibility criteria included patients who had a previous history of cancer treatment (tumour resection, chemotherapy, immunotherapy, or radiotherapy) before entry into the study, in actuality no patients had previously received such treatment.

Table 1 Patient characteristics

Patients enrolled	21
Men	10
Women	11
Age, years	
Median	61
Range	48–73
ECOG status	
0	8
1	11
2	2
Sites of metastatic disease	
Liver	18
Lung	3
Peritoneum	2

Table 2 Dose levels

Dose level	S-1 (mg m^{-2} day^{-1}: 2 weeks)	Gemcitabine (mg m^{-2}: on days 8, 15)	No. of patients
1	60	800	3
2a	80	800	6
2b	60	1000	12

The numbers of patients at each level are shown in Table 2. Three patients were assigned to dose level 1 without DLT. At dose level 2a, DLT was observed in two of the first three patients; thus three additional patients were assigned to this level. Dose-limiting toxicity was observed in three of six patients, and level 2a reached MTD. Thus, three patients were assigned to level 2b and no DLT was observed in the first three patients. However, nine additional patients were assigned to this level to explore the responses to and continuity of the treatment.

Toxicity and treatment cycles

The most common toxicities observed during the first cycle of chemotherapy are listed in Tables 3 and 4. Of three patients in level 1, one had thrombocytopenia of grade 3, but no DLT leading to MTD was observed in any patient. Of six patients in level 2a, grade 3–4 neutropenia occurred in four patients, grade 3 anaemia in one patient and grade 3 thrombocytopenia in two patients. In terms of nonhaematological toxicities, grade 4 anorexia, grade 3 nausea and grade 3 rash occurred in one patient, each. Three of six patients at level 2a showed DLT; one patient developed sepsis with grade 4 leukopenia and neutropenia, a second patient developed a grade 3 rash and a third patient developed grade 2 leukopenia, not recovering within the planned period. Thus, DLT was observed in three of six patients, and level 2a reached MTD. Of 12 patients at level 2b, grade 3 to 4 neutropenia occurred in three patients and grade 3 anaemia in one patient, while grade 3 anorexia occurred in one patient, and DLT leading to MTD was not observed. Based on these results, level 2b was selected as the RD for the phase II study we are to conduct.

The median and range of the treatment cycles and the number of patients who received a dose reduction were shown in Table 5. The median number of cycles delivered at dose level 2b, which was selected as the RD, was four, and only six of 61 cycles at this dose level needed to reduce their dose of gemcitabine.

Efficacy

Although assessment of tumour response was not a primary objective of this study, patients were evaluated for tumour response every two cycles (6 weeks) of the treatment. All 21 patients were assessed for response during this treatment. Responses in the 21 assessable patients were: one CR (dose level 2a), nine PRs (one at dose level 1, three at dose level 2a and five at dose level 2b), six stable disease (two at dose level 1, one at dose level 2a, and three at dose level 2b) and progression in only five patients (one at dose level 2a and four at dose level 2b). As a result, 10 of the 21 patients (48%) showed complete or PRs (Table 6). The value of CA 19-9 before treatment was elevated (>37 U l^{-1}) in 15 of 21 patients. Of those 15 patients, CA 19-9 decreased 50% or more compared with the level prior to treatment in seven (47%) and showed a normal value in three (20%). In contrast, an increase of CA 19-9 was observed in only four patients (27%). At present, seven patients are still alive. After a median follow-up of 8.9

Table 3 Haematological toxicity during first cycle (in all cycles)

		No. of patients (cycles) with grade of toxicity						
		Neutropenia		Anaemia		Thrombocytopenia		
Dose level	Total no. of patients (cycles)	1–2	3–4	1–2	3–4	1–2	3–4	DLT
1	3 (27)	2 (13)	0 (5)	3 (5)	0 (1)	2 (6)	1 (5)	
2a	6 (66)	2 (34)	4 (22)	5 (15)	1 (5)	4 (13)	2 (13)	2
2b	12 (61)	7 (25)	3 (6)	5 (8)	1 (2)	11 (13)	0 (0)	