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Contrast-enhanced harmonic endoscopic ultrasonography for evaluating the response to chemotherapy in pancreatic cancer

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ABSTRACT

Background and aims: Contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS) is used for the diagnosis of pancreatic cancer (PC). Here, we examined the usefulness of CH-EUS for evaluating therapeutic responses in PC.
Methods: The study included 23 patients with PC who received chemotherapy. Patients underwent contrast-enhanced computed tomography (CE-CT) and CH-EUS before chemotherapy and at the time of evaluation of the therapeutic response. Patients with a ≧50% reduction in serum carbohydrate antigen 19–9 levels after chemotherapy were defined as "super responders". The incidence of an avascular area in the tumor on CH-EUS after chemotherapy was compared between "super responders" and non-super responders.
Results: Nine patients were included in the "super responders" group.Tumor reduction rates did not differ significantly between CE-CT and CH-EUS in the "super responders". The appearance of an avascular area was detected in 7 of 9 super responders (77.8%) and in 4 of 14 non-super responders (28.6%), and the difference was significant (P = 0.036). The mean survival time of patients with an avascular area after chemotherapy was longer than that of without an avascular area.
Conclusions: Detection of avascular areas by CH-EUS after chemotherapy may predict long-term survival of patients with PC.

1. Introduction

Pancreatic cancer (PC) is one of the deadliest cancers with a 5-year survival rate of 5% [1]. Although complete surgical resection is the only curative treatment for PC, less than 20% of patients undergo surgical resection [1]. The majority of patients with PC require chemotherapy from the time of diagnosis because surgical treatment alone does not improve survival [2]. PC is diagnosed by several imaging modalities including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS) [3]. In particular, contrast-enhanced CT (CE-CT) is essential for the diagnosis and determination of treatment policy in PC [3]. CE-CT is used for evaluating the response to chemotherapy in patients with PC according to RECIST guidelines (ver. 1.1) [4] and CHOI criteria [5], which are determined based on changes in tumor diameter and CT values. Previous work from our group recommended the use of contrast-enhanced US (CE-US) for evaluating the response to chemotherapy in PC [6]. However, contrast-enhanced harmonic EUS (CH-EUS) recently emerged as a promising tool for the diagnosis of pancreatic diseases [7–11]. CH-EUS is superior to US for detecting PC [7–11]. In the present study, we compared the abilities of CH-EUS and CT to measure reductions in tumor size. A previous report showed that avascular areas on CE-US in patients with PC are related to severe fibrosis and necrosis within the lesion [12]. In previous work from our group, evaluation of avascular areas using CH-EUS showed that EUS-guided fine needle aspiration has low sensitivity in PC patients with avascular areas

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Table 1
Patient characteristics.

Total	n = 23
Mean age, y (range)	62.9 (34–80)
Male/female, n	10/13
Mean tumor size by CE-CT mm, (range) (before chemotherapy)	57.6 (18.6–96.3)
Mean tumor size by CE-CT, mm, (range) (after chemotherapy)	48.1 (20.6–87.4)
Mean tumor size on CH-EUS, mm, (range) (before chemotherapy)	55.7 (22.0–90.4)[a]
Mean tumor size on CH-EUS, mm, (range) (after chemotherapy)	49.5 (19.5–73.0)[a]
TNM classification	
T3N1M0	1
T3N0M1	1
T4N0M0	12
T4N1M0	2
T4N0M1	5
T4N1M1	2
PR/SD/PD (RECIST v1.1)	4/16/3
PR/SD/PD (CHOI criteria)	9/10/4
Surgical cases after chemotherapy, n	3
Appearance of avascular area, n	11
Location of pancreatic cancer (head/body and tail)	8/15
Distant metastasis, n	8
Mean treatment duration, days, (range)	169.1 (61–598)[b]
Regimen of chemotherapy, n (GEM/TS1/GEM + TS1/FOLFIRINOX/ GEM + nab-PTX)	18/1/1/1/2

CE-CT; contrast-enhanced computed tomography, CH-EUS; contrast-enhanced harmonic endoscopic ultrasonography, FOLFIRINOX; fluorouracil, leucovorin, irinotecan and oxaliplatin, GEM; gemcitabin, GEM + nab-PTX; gemcitabine + nab-Paclitaxel, GEM + TS1; gemcitabine + Tegafur, Gimeracil, Oteracil, SD; stable diseases, PD; progressive diseases, PR; partial response, TS1; Tegafur, Gimeracil, Oteracil.

[a] Mean tumor sizes determined by CH-EUS before (P = 0.347) and after (P = 0.714) chemotherapy were compared with those determined by CE-CT using the t-test.

[b] Treatment duration was defined as the period from the time of CH-EUS before chemotherapy to evaluation of the therapeutic response.

on CH-EUS, indicating that the avascular area indicates the presence of necrosis [13]. This suggests that the appearance of an avascular area after chemotherapy in patients with PC in the present study was related to cancer cell necrosis induced by chemotherapy. Thus, the appearance of an avascular area in the tumor on CH-EUS after chemotherapy and its prognostic significance were assessed.

2. Patients and methods

2.1. Study design

The present study was a single-center retrospective study. CH-EUS was performed by expert endoscopists. The present study was performed with the approval of the ethics committee of Kindai University Faculty of Medicine.

2.2. Patients

The study enrolled 23 patients (mean age, 62.9 years; male to female ratio, 13:10) with PC who underwent chemotherapy in Kindai University Hospital between April 2010 and March 2016 (Table 1). Eighteen out of 23 patients underwent gemcitabine monotherapy. CH-EUS was performed at the same time as CE-CT (within 2 weeks) before chemotherapy and at the time of evaluation of the therapeutic response. No patient showed an avascular area on CH-EUS before chemotherapy

2.3. Contrast-enhanced computed tomography

Intravenous CE-CT imaging was performed using two-phase CT (Toshiba X-vigor; Toshiba Medical System, Tokyo, Japan) or a 64-channel multidetector CT scanner (Light Speed VCT Vision: GE Healthcare, Milwaukee, Wisconsin, USA) with a 5.0 mm image thickness. In the former modality, 100 mL of Iopamiron (iopamidol; Nihon Schering, Osaka, Japan), with an iodine concentration of 370 mg/mL, was injected. Dynamic acquisition was performed in the early arterial phase (30 s) and portal phase (60 s). In the latter modality, 510 mg of iodine per kg of iodinated contrast material was administered intravenously at a rate of 3–4 mL/s. Scanning was performed during the pancreatic parenchymal phase (at 40 s) and the liver phase (at 70 s) [14].

2.4. Contrast-enhanced harmonic endoscopic ultrasonography

The echoendoscope used for CH-EUS was GF-UCT260 (Olympus Medical Systems Co Ltd, Tokyo, Japan), and the EUS images were analyzed using an Aloka ProSound SSD a-10 system (ALOKA Co Ltd, Tokyo, Japan). An extended pure harmonic detection (ExPHD) mode was used; this synthesized the filtered second harmonic components with signals obtained from the phase shift to provide contrast-enhanced harmonic imaging [9,10,15]. A conventional EUS examination was performed initially. When conventional EUS depicted the pancreatic tumor, the imaging mode was changed to ExPHD mode. The transmitting frequency and mechanical index were 4.7 MHz and 0.3, respectively. Sonazoid (Daiichi-Sankyo, Tokyo, Japan) with a dose of 15 mL/kg body weight was used as an ultrasound contrast agent for CH-EUS. Two experienced endosonographers (K.K. and M.K.), who performed more than 1000 CH-EUS procedures each, participated in the study. CH-EUS examinations for PC lasted 60 s from the time of injection of the contrast agent. Video sequences of 60 s were stored. For the retrospective review of stored data, the readers were blinded to the clinical findings. Diagnosis of avascular area and measurement of the maximum size of each avascular area were performed simultaneously in consultation with two readers during the special review of videos. Therefore, the Kappa value of the two readers for the diagnosis of avascular areas was not calculated in the study.

2.5. Definitions

Tumor diameters on CE-CT and CH-EUS and serum carbohydrate antigen 19–9 (CA19-9) levels were measured before chemotherapy and at the time of evaluation of the therapeutic response within 2 weeks. Responses to chemotherapy were classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to RECIST guidelines (ver. 1.1) and CHOI criteria. Tumor reduction rate was calculated by both CE-CT and CH-EUS as (tumor size before chemotherapy minus tumor size after chemotherapy) divided by tumor size before chemotherapy. As previously reported, CA19-9 is the most extensively studied and validated serum biomarker for pancreatic cancer. Normalization or a decrease in post-operative CA19-9 serum levels by >20–50% from baseline following surgical resection or chemotherapy is associated with prolonged survival when compared with an increase in serum of CA19-9 or failure to normalize [16]. Therefore, we classified the patients showing a ≥50% reduction in serum CA19-9 levels after chemotherapy as "super responders". The avascular area on CH-EUS was defined as the presence of a non-enhancing area in the tumor (Fig. 1) [15]. A video of each CH-EUS examination for PC lasting 60 s from the time of injection of the contrast agent was recorded. Avascular area were evaluated in the perfusion phase (40–60 s), and the maximum diameter was measured. No special software was used to calculate the mean contrast enhancement during the exam. Two expert endosonographers (K.K. and M.K.), who performed more than 1000 CH-EUS procedures each, performed CH-EUS and evaluated the avascular areas. Twenty-three patients were classified into two groups as follows: "Without avascular area" = no appear-

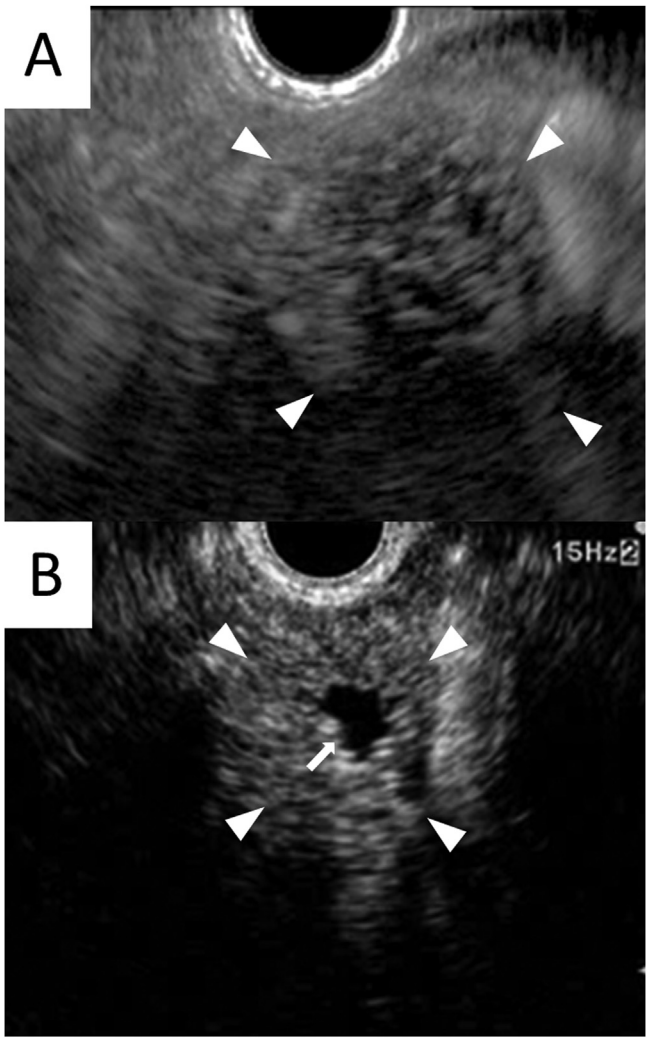

Fig. 1. CH-EUS images obtained before (A) and after (B) chemotherapy showing reduced tumor size (arrowheads) and the appearance of an avascular area after chemotherapy (B, arrow).

ance of an avascular area after chemotherapy; "With avascular area" = appearance of an avascular area after chemotherapy.

2.6. Statistical analysis

The comparison of mean tumor sizes in all patients and in the group of "super responders" between CE-CT and CH-EUS was evaluated using the t-test. Mean tumor reduction rates in the "super responders" group were compared between CE-CT and CH-EUS using the t-test. The rates of appearance of avascular areas on CH-EUS after chemotherapy were compared between "super responders" and remaining patients using Fisher's exact test. $P < 0.05$ was considered statistically significant. Median survival times (MST) were compared between groups using the Kaplan–Meier method. For this analysis, the P value was not calculated because the number of patients in each group was too small. All statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

3. Results

Patient characteristics are shown in Table 1. Among the 23 patients examined, distal metastasis was observed in eight. PR was observed in four, SD in 16, and PD in three patients (according to RECIST criteria). PR was observed in nine, SD in ten, and PD in four patients (according to CHOI criteria). Nine patients were classified as "super responders". Among super responders, three showed PR and six showed SD (defined according to RECIST criteria), whereas according to DHOI criteria, there were five PR, three SD, and one PD patient. The mean tumor diameters before chemotherapy and at the time of evaluation of therapeutic response in the overall cohort were 57.6 and 48.1 mm for CE-CT and 55.6 and 49.5 mm for CH-EUS, respectively; in addition, there was no significant difference between tumor sizes evaluated by CE-CT and CH-EUS. The mean treatment duration was 169.1 days (Table 1). In the "super responders" group, there was no significant difference between tumor sizes evaluated by CE-CT and CH-EUS (Table 2). There was no significant difference in tumor reduction rates between CE-CT and CH-EUS in the group of "super responders" (Table 2).

Table 2
Comparison of tumor sizes and reduction rates in super responders between CE-CT and CH-EUS.

Super responders	CE-CT	CH-EUS	P value[a]
Mean tumor size, mm, (range) (before chemotherapy)	54.8 (18.6–96.3)	49.8 (22.0–90.4)	0.168
Mean tumor size, mm, (range) (after chemotherapy)	40.4 (20.6–54.0)	40.0 (19.5–73.0)	0.909
Mean tumor reduction rate, %	−17.3	−12.0	0.516

CE-CT; contrast-enhanced computed tomography, CH-EUS; contrast-enhanced harmonic endoscopic ultrasonography.
[a] Comparison between CE-CT and CH-EUS was evaluated using the t-test.

Table 3
Number of patients with or without the appearance of an avascular area on CH-EUS after chemotherapy in super responders and in the others.

Avascular area after chemotherapy	Super responders	Others	Total
Appearance	7	4	11
No appearance	2	10	12
Total	9	14	23

CH-EUS; contrast-enhanced harmonic endoscopic ultrasonography.
The number of patients showing the appearance of an avascular area was compared between super responders and the others ($P = 0.036$, Fisher exact test).

The appearance of an avascular area on CH-EUS after chemotherapy was confirmed in 11 of 23 patients (47.8%), whereas it was not detected by CE-CT in all patients. According to RECIST v1.1, there were two PR and nine SD patients, whereas according to CHOI criteria, there were five PR, five SD, and one PD patient.

Each patient had only one avascular area. The average diameter of the avascular area was 3.9 mm (range: 2.8–4.6 mm). The appearance of the avascular area was detected in 7/9 super responders (77.8%) and in 4/14 non-super responders (28.6%), and the difference was significant ($P = 0.036$) (Table 3).

The MSTs of "Without avascular area" and "With avascular area" groups were 12.1 and 45.6 months, respectively. This is a result with a small number of patients ($n = 23$), the MST of the "With avascular area" group was longer than that of the "Without avascular area" group (Fig. 2). Surgical resection was performed in 3/ 23 patients. Among them, two patients showed long-term progression-free survival (PFS) (1387 and 1205 days), whereas the PFS of the remaining patient was 438 days. The two patients with long-term PFS showed the appearance of an avascular area on CH-EUS. These patients were defined as PR (according to RECIST and CHOI criteria).

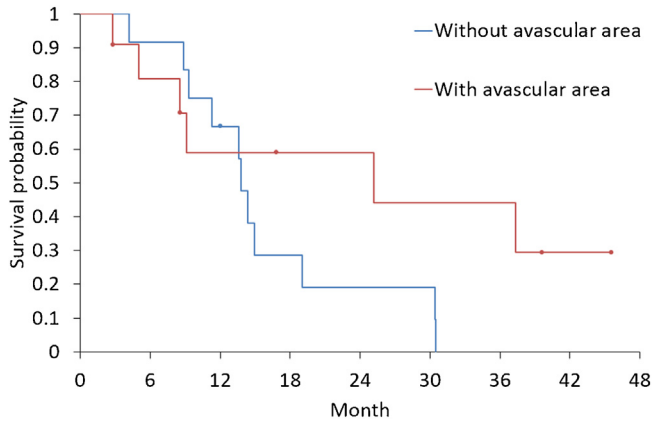

Fig. 2. Kaplan–Meier survival curve of 23 patients divided into two groups*. *"Without avascular area" = no appearance of an avascular area after chemotherapy; "With avascular area" = appearance of an avascular area after chemotherapy.

4. Discussion

For many patients presenting with the common symptoms of PC, abdominal US is a reasonable first imaging test. However, in cases in which a diagnosis of PC cannot be made based on US results despite the presence of findings highly suggestive of PC on clinical examination, CE-CT is performed as a standard imaging method for the diagnosis and staging of PC [13,17]. CE-CT involves triphasic (i.e., arterial, late, and venous phases) cross-sectional imaging that allows for enhancement between the parenchyma and adenocarcinoma [18]. Because CE-CT can detect distant metastasis of PC, such as those in the liver, lung and lymph nodes, it is a useful tool for PC staging. CE-CT is also used for evaluating the response to chemotherapy according to the RECIST criteria and CHOI criteria.

In a previous study including a small number of patients, we showed that CE-US was more effective for evaluating the response to chemotherapy than CE-CT. The results of that study showed that CE-US could identify apparent differences in vascularity between normal and tumor regions, and was superior to CE-CT for evaluating the response to chemotherapy in PC [6]. In the previous study, we examined differences in tumor reduction rates between CE-US and CE-CT in six patients showing a reduction in tumor marker values (CEA, CA19-9, DUPAN-2, and S-pancreas-1) of 50% or more. The tumor reduction rate detected by CE-US was significantly greater CE-US than that by CE-CT, suggesting that CE-US is more effective for evaluating differential responses to chemotherapy than CE-CT. However, in the present study, the tumor marker used for determining "super responders" was limited to CA19-9; this might explain the lack of significant differences in tumor reduction rates between CE-CT and CH-EUS in the "super responders" group.

One of the limitations of CE-US is that it can only be used in cases of visible tumors on US. On the other hand, EUS is significantly more accurate than US or CT and is especially useful for detecting small PCs of less than 2 cm in diameter [9,19]. A systemic review of 30 studies with 1554 patients indicated that EUS is superior to CT for identifying vascular involvement [20]. The sensitivity of EUS and CT was 72% and 63%, respectively, and the specificity was 89% and 92%, respectively. Another meta-analysis showed that EUS has a sensitivity of 91% and a specificity of 94% for identifying vascular involvement [21]. Therefore, we used CH-EUS to evaluate the therapeutic response to chemotherapy in the patients with PC.

In the present study, the appearance of an avascular area on CH-EUS was detected in 11 of 23 (47.8%) patients with PC after chemotherapy. There are several reports describing the avascular area of PC [15,22,12]. One report showed that the MST of patients with PC was significantly lower in those with an avascular area on CE-US than in those without [22]. By contrast, we detected the avascular area on CH-EUS after chemotherapy, not before chemotherapy. Another report showed that tumor avascular areas on CE-US in patients with PC were related to severe fibrosis and necrosis within the lesion [12]. In previous work from our group, evaluation of avascular areas using CH-EUS showed that EUS-guided fine needle aspiration had a lower sensitivity in PC patients with avascular areas on CH-EUS, indicating that the avascular area represents the presence of necrosis [13]. This suggests that the appearance of an avascular area after chemotherapy in patients with PC in the present study is related to cancer cell necrosis induced by chemotherapy. In fact, the "With avascular area" group had a longer MST than the other group. Therefore, the appearance of an avascular area detected by CH-EUS after chemotherapy could be a new predictor of long-term survival in patients with PC who underwent chemotherapy.

The present study had several limitations. The study used a retrospective design and included a small number of patients. Only three patients without distal metastasis who showed a PR underwent surgery after chemotherapy, and avascular areas detected by CH-EUS were not pathologically investigated using surgical specimens. The "super responders" group was defined by a $\geq$ 50% reduction in CA19-9; however, is not clear whether this definition is appropriate.

In conclusion, CH-EUS is a feasible method for evaluating the response to chemotherapy according to tumor size, and its efficacy is equivalent to that of CE-CT. The appearance of avascular areas detected by CH-EUS after chemotherapy might predict the long-term survival of patients with PC. Therefore, CH-EUS might be an alternative modality for evaluating tumor reduction in patients who are allergic to contrast agents. Moreover, we might choose a more suitable treatment strategy including conversion surgery after the response evaluation by CH-EUS. Further studies including a larger patient cohort are warranted to validate the results of the present study.

Conflict of interest

None declared.

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Guarantor of the manuscript

Ken Kamata.

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