European Radiology (2019) 29:353–361
https://doi.org/10.1007/s00330-018-5570-4

HEPATOBILIARY-PANCREAS

Extracellular volume fraction determined by equilibrium contrast-enhanced multidetector computed tomography as a prognostic factor in unresectable pancreatic adenocarcinoma treated with chemotherapy

Yoshihiko Fukukura[1] · Yuichi Kumagae[1] · Ryutaro Higashi[1] · Hiroto Hakamada[1] · Koji Takumi[1] · Kosei Maemura[2] · Michiyo Higashi[3] · Kiyohisa Kamimura[1] · Masanori Nakajo[1] · Takashi Yoshiura[1]

Received: 10 January 2018 / Revised: 14 May 2018 / Accepted: 28 May 2018 / Published online: 19 June 2018

Abstract

Objectives To assess whether extracellular volume (ECV) fraction with equilibrium contrast-enhanced multidetector computed tomography (MDCT) predicts outcomes for unresectable pancreatic adenocarcinoma patients treated with chemotherapy

Methods Sixty-seven patients (42 men, 25 women; mean age, 67.5 years; range, 45–83 years) with histologically confirmed surgically unresectable pancreatic adenocarcinoma underwent contrast-enhanced MDCT before systemic chemotherapy. Tumour contrast enhancement (CE) and ECV fraction were calculated using region-of-interest measurement within the pancreatic adenocarcinoma and aorta on unenhanced and equilibrium phase-enhanced CT. The effect on survival variables including age, sex, tumour location, tumour size, TNM stage, carbohydrate antigen (CA) 19-9, carcinoembryonic antigen (CEA), tumour CE and tumour ECV fraction was determined on univariate and multivariate analyses using Cox proportional hazards regression model.

Results Median overall survival was 10.5 months. On univariate analysis, elevated serum CA19-9 (hazard ratio (HR), 1.00; $p = 0.006$) and CEA (HR, 1.02; $p = 0.011$) levels were found to be associated with a negative effect on overall survival. Increasing tumour CE (HR, 0.98; $p < 0.001$) and ECV fraction (HR, 0.97; $p = 0.001$) were associated with a positive effect. Multivariate analysis revealed that only tumour ECV fraction was an independent predictor of overall survival (HR, 0.97; $p = 0.012$).

Conclusions ECV fraction with equilibrium contrast-enhanced MDCT could be a useful imaging biomarker for predicting patient survival after chemotherapy for unresectable pancreatic adenocarcinoma.

Key Points

- *Tumour aggressiveness and response to therapy are influenced by the extravascular extracellular space.*
- *Extracellular volume (ECV) fraction can be quantified with equilibrium contrast-enhanced CT.*
- *Patients with higher tumour ECV fraction had better prognosis after chemotherapy.*

Keywords Pancreas cancer · Multidetector computed tomography · Contrast media · Extracellular space · Treatment outcome

✉ Yoshihiko Fukukura
fukukura@m.kufm.kagoshima-u.ac.jp

[1] Department of Radiology, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima City 890-8544, Japan

[2] Digestive Surgery, Breast and Thyroid Surgery, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima City 890-8544, Japan

[3] Human Pathology, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima City 890-8544, Japan

Abbreviations

CA	Carbohydrate antigen
CE	Contrast enhancement
CEA	Carcinoembryonic antigen
ECV	Extracellular volume
FDG-PET	^{18}F-Fluorodeoxyglucose positron emission tomography
ICC	Intraclass correlation coefficient
MDCT	Multidetector computed tomography
ROIs	Regions of interest
UICC	International Union Against Cancer

Introduction

Pancreatic adenocarcinoma is the most frequent and lethal form of pancreatic cancer. It represents the fourth leading cause of cancer-related deaths in the most developed countries [1, 2]. It is a highly lethal disease with a 5-year survival rate of < 10% [2, 3]. Only margin-negative surgical resection may be a potentially curative treatment for this condition. Despite recent advances in diagnostic techniques, > 80% of patients are diagnosed at an advanced, surgically unresectable stage [2]. Recent developments in chemotherapy have helped improve the prognosis of patients with unresectable pancreatic adenocarcinoma [4, 5]. However, we experienced much variability regarding treatment outcomes even with the use of identical chemotherapy regimens in different patients. While some patients show improvement in survival, others do not improve and have increased toxicity. Therefore, identifying reliable preoperative imaging biomarkers for surgically unresectable pancreatic adenocarcinoma is a key imperative that may help adapt treatment approaches.

Dynamic contrast-enhanced CT and MR imaging allow for quantitative estimation of various haemodynamic parameters such as volume transfer constant, extravascular extracellular volume fraction and intravascular space fraction. These indices reflect the structural and vascular features of the target tissue and have been used as prognostic biomarkers for various cancers [6–10]. The extravascular extracellular volume fraction in malignant pancreatic solid lesions quantified by dynamic contrast-enhanced MR imaging significantly correlates with fibrosclerotic stroma, which confers treatment resistance and promotes malignant growth and metastasis [11, 12]. However, the use of dynamic contrast-enhanced CT and MR imaging is technically demanding and requires multiple repeat studies that are difficult to perform for routine clinical studies.

The extracellular volume (ECV) fraction is the sum of the extravascular extracellular volume fraction and intravascular space fraction. In recent studies, ECV fraction determined by equilibrium contrast-enhanced CT or MR imaging was associated with cardiac [13, 14] and hepatic fibrosis [15–17]. Benjaminsen et al [18] reported that ECV fraction in human melanoma xenografts, measured by contrast-enhanced MR imaging, was positively correlated with extravascular extracellular volume fraction determined by histological analysis. We speculated that ECV fraction of the tumour tissue quantified with equilibrium contrast-enhanced CT or MR imaging that can be easily integrated into routine examinations is an important prognostic parameter for patients with malignant diseases. To our knowledge, the clinical relevance of ECV fraction with equilibrium contrast-enhanced CT or MR imaging as an imaging biomarker for patients with cancer has not been reported.

The purpose of this study was thus to assess whether ECV fraction with equilibrium contrast-enhanced multidetector computed tomography (MDCT) predicts outcomes for unresectable pancreatic adenocarcinoma patients treated with chemotherapy.

Materials and methods

Patient population

The institutional review board of our hospital approved this retrospective study; the requirement for informed consent was waived off. Between January 2009 and December 2016, 1,902 consecutive patients underwent quadriphasic CT (including unenhanced, pancreatic parenchymal, portal venous and delayed phases) for the evaluation of suspected pancreatobiliary diseases based on previous ultrasonography or CT. These patients were retrospectively identified through a review of our CT database and records at the Department of Radiology. The following inclusion criteria were used to select the study population: (i) pathological diagnosis of pancreatic ductal adenocarcinoma; and (2) unresectable tumour treated with first-line gemcitabine and S-1 combination chemotherapy. Of these, 442 patients were diagnosed with pancreatic ductal adenocarcinoma based on histopathological examination of surgical or biopsy specimens. Seventy-two patients with unresectable tumours received 1,000 mg/m^2 gemcitabine intravenously over 30 min on days 1 and 8, and 40 mg/m^2 S-1 orally twice daily on days 1–14, every 3 weeks. This cycle was repeated until disease progression was detected or unacceptable toxicity was observed. As a result, 72 patients met our inclusion criteria. Two patients who underwent chemotherapy (n = 1) or surgical resection (n = 1) prior to CT were excluded. We also excluded three patients because of inadequate follow-up (< 6 months). The final study population consisted of 67 patients (42 men, 25 women; mean age, 67.5 years; range, 45–83) (Fig. 1).

Data pertaining to the following clinical and biochemical variables were retrieved (by YF with 24 years of experience in abdominal radiology): age; sex; treatment and follow-up; haematocrit level; and serum levels of tumour markers including carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA), which were measured within 1 week of the CT (mean, 0.8 days; range, 0–6 days). Two radiologists (HH and KT with 12 and 15 years of experience in abdominal radiology, respectively) retrospectively determined the tumour location, size and TNM stage according to International Union

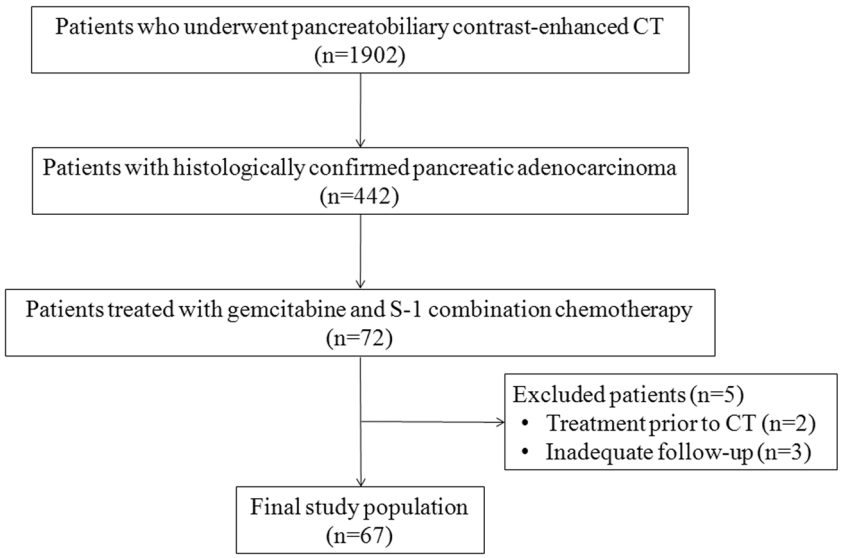

Fig. 1 Flow diagram for 67 patients with unresectable pancreatic adenocarcinoma treated with gemcitabine and S-1 combination chemotherapy

Against Cancer (UICC) classification of pancreatic adenocarcinoma on CT (n = 67), MR imaging (n = 53) and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) (n = 46) by consensus. Apart from knowledge of the final diagnosis (pancreatic adenocarcinoma), both observers were blinded to clinical information, including tumour markers, and patient outcomes. Local tumour extension beyond the pancreas was diagnosed when no normal pancreatic tissue was observed between the tumour and the peritumoral structures. Tumorous involvement of the coeliac axis or superior mesenteric artery was considered if more than one-half of the circumference of the artery was found contiguous with the tumour [19]. The presence of lymph node metastases was defined as lymph nodes with a short-axis diameter of > 10 mm [20].

CT imaging technique

CT was performed using 64-detector row CT scanners (Aquilion; Toshiba Medical Systems, Tokyo, Japan). All scans began at the top of the liver and went through to the end of the pancreas. Imaging parameters for all phases were as follows: tube voltage, 120 kVp; gantry rotation speed, 0.5 s; maximum allowable tube current, 440 mA; detector row configuration, 64 × 0.5 mm; table increment, 26.5 mm/rotation; matrix, 512 × 512; and reconstructed into 3-mm-thick axial sections with a standard soft-tissue kernel (FC 13). On the basis of a preset noise index of 11.5 HU for a 3-mm slice thickness, the tube current was automatically modulated (Volume Exposure Control, Toshiba Medical Systems) during CT across the anatomical regions. Pancreatic parenchymal and portal venous phase scans were obtained using a 20- and 48-s delay after the aortic enhancement exceeded 150 HU compared to baseline, respectively. Scan delay for the equilibrium phase was fixed at 180 s after intravenous injection of 1.7 ml/kg body weight of nonionic contrast material with an iodine concentration of 350 mgI/ml (Iomeron; Eisai, Tokyo, Japan) at a fixed duration of 25 s.

Image analysis

Attenuation values on unenhanced CT and the equilibrium phase of enhanced CT for all pancreatic adenocarcinomas were independently obtained by two radiologists (YK and RH with 15 and 17 years of experience in abdominal radiology, respectively) who did not attend the reading sessions and were blinded to clinicopathological data; however, the radiologists were aware of the location and size of pancreatic adenocarcinoma. Circular or oval regions of interest (ROIs) were placed as large as possible within the pancreatic adenocarcinoma (mean size, 162.2 mm^2; range, 40–747 mm^2) and the aorta at the level of the pancreatic adenocarcinoma (approximately 100 mm^2). An attempt was made to place the ROIs in identical sites for unenhanced and equilibrium phase CTs for each patient. The values measured by the two observers were averaged to represent each ROI. The contrast enhancement (CE) and ECV fraction of pancreatic adenocarcinoma were calculated using the following equation: CE (HU) = ΔHU_{tumor} and ECV fraction (%) = (1 − haematocrit) × ($\Delta HU_{tumor}/\Delta HU_{aorta}$) × 100, respectively, where ΔHU_{tumor} and ΔHU_{aorta} are HU in equilibrium phase minus HU before contrast agent administration of the tumour and the aorta, respectively.

Statistical analysis

Intraclass correlation coefficient (ICC) was calculated to evaluate inter-observer agreement for CE and ECV fraction (ICC

= 0.00–0.20, poor correlation; ICC = 0.21–0.40, fair correlation; ICC = 0.41–0.60, moderate correlation; ICC = 0.61–0.80, good correlation; ICC = 0.81–1.00, excellent correlation) [21].

Patient survival was determined from the date of CT to the date of most recent follow-up examination or date of death. The last date of data collection was July 2017. Overall survival curves were generated using the Kaplan–Meier method. The effect on survival of variables including age, sex, tumour location, tumour size, TNM stage, serum CA 19-9 and CEA levels, and CE and ECV fraction of the primary lesion was assessed on univariate and multivariate analyses using Cox proportional hazards model. Pearson correlation analysis examined possible multicolinearity between tumour CE and ECV fraction before the multivariate analysis.

Receiver-operating characteristic curve analysis was performed to determine the optimal cut-off values of tumour CE and ECV fraction for predicting 1-year outcome of patients. The sensitivity and specificity of tumour CE and ECV fraction were calculated by using the cut-off values, which were identified by determining the value where the sum of sensitivity and specificity was maximal. The Kaplan–Meier method with the log-rank test was generated to assess overall survival in subjects with tumour CE and ECV fraction above and below the optimal ROC-derived cut-off values.

Continuous variables were expressed as the mean ± standard deviation. *P* values < 0.05 were considered indicative of a statistically significant difference. All statistical analyses were performed using JMP version 9 software (SAS Institute Japan, Tokyo, Japan).

Results

Patient characteristics

Lesions were located in the head (n = 37), body (n = 22) or tail (n = 8) of the pancreas; maximum diameter ranged from 10 mm to 74 mm (mean, 38.4 mm; median, 36 mm). According to the UICC classification, 16 patients were in Stage IIA, 3 patients in Stage IIB, 11 patients in Stage III and 37 patients in Stage IV. Serum levels of tumour markers CA 19-9 and CEA were elevated in 54 patients (80.6%) and 28 patients (41.8%), respectively. The CE and ECV fraction of pancreatic adenocarcinoma were 39.4 ± 17.3 HU (range, 9–80 HU; median, 36.8 HU) and 29.9 ± 13.6% (range, 7.6–62.4%; median, 28.1%), respectively. Inter-observer agreement was excellent; ICCs for CE was 0.94 and that for ECV fraction was 0.93.

Survival

Follow-up periods in the entire study cohort ranged from 6.9 to 103.4 months (median, 45.7 months), while median duration of follow-up among the eight survivors was 19.9 months (range, 12.3–76.2 months). Fifty-nine patients experienced cancer-related death between 0.7 to 38.9 months (median, 9.6 months). Median overall survival was 10.5 months (95% confidence interval (CI): 8.8–12.8).

Univariate and multivariate analyses

Table 1 lists the results of univariate and multivariate analyses. Univariate analysis showed no significant influence of patient age ($p = 0.509$), sex ($p = 0.879$), tumour location ($p = 0.127$), tumour size ($p = 0.177$) or TNM stage ($p = 0.181$) on patient survival. On univariate analysis, elevated serum CA19-9 (hazard ratio (HR), 1.00; 95% CI: 1.00–1.00; $p = 0.006$) and CEA levels (HR, 1.02; 95% CI: 1.00–1.03; $p = 0.011$) were found to be associated with poor patient survival. Increasing tumour CE (HR, 0.98; 95% CI: 0.96–0.99; $p < 0.001$) and ECV fraction (HR, 0.97; 95% CI: 0.95–0.99; $p = 0.001$) were associated with a positive effect on overall survival. Tumour CE and ECV fraction were significantly correlated (correlation coefficient = 0.93, all $p < 0.001$), and thus the tumour CE was excluded from multivariate analysis due to multicollinearity. On multivariate analysis, only tumour ECV fraction showed an independent predictor of overall survival in patients with unresectable pancreatic adenocarcinoma treated with chemotherapy (HR, 0.97; 95% CI: 0.95–0.99; $p = 0.012$).

The optimal cut-off values were 43.0 HU for tumour CE and 28.0% for tumour ECV fraction to differentiate patients who survived more than 1 year (n = 32) from those who did not (n = 35). For predicting 1-year survivor, sensitivity and specificity were 65.6% (21/32) and 85.7% (30/35) with tumour CE, and 75.0% (24/32) and 77.1% (27/35) with tumour ECV fraction, respectively. Patients with higher tumour CE survived longer than those with lower tumour CE ($p < 0.001$), when stratified by the cut-off value (43.0 HU). Median survival time for patients with tumour ECV fraction of ≥ 28.0% was 15.2 months (Fig. 2), as opposed to 8.4 months for patients with tumour ECV fraction of < 28.0% (Fig. 3). The difference between groups divided by the cut-off value of 28.0% was significant ($p < 0.001$) (Fig. 4).

Discussion

Equilibrium contrast-enhanced CT or MR quantification of ECV fraction is used to explore heart [13, 14] and liver fibrosis [15–17] and to assess amyloid protein deposition in the heart, liver and spleen [22–24]. However, no attempts have been made to employ ECV fraction for oncological assessment. In this retrospective study, we measured tumour ECV fraction using equilibrium contrast-enhanced CT examination before chemotherapy in patients with unresectable pancreatic adenocarcinoma. We found that a simple quantitative CT

Table 1 Overall survival in patients with unresectable pancreatic adenocarcinomas

Variable	Patients	Univariate analysis		Multivariate analysis	
		Hazard ratio	*p*	Hazard ratio	*p*
Age (years)		0.99 (0.96–1.02)	0.509	0.99 (0.96–1.03)	0.712
Sex			0.879		0.731
Male	42	1.0		1.0	
Female	25	0.96 (0.55–1.62)		0.90 (0.49–1.63)	
Tumour location			0.127		0.398
Head	37	1.0		1.0	
Body to tail	30	1.50 (0.89–2.51)		1.32 (0.69–2.54)	
Tumour size (mm)		1.95 (0.73–4.98)	0.177	0.99 (0.97–1.02)	0.555
TNM stage			0.181		0.765
II	19	1.0		1.0	
III	11	1.36 (0.58–3.04)		1.19 (0.47–2.93)	
IV	37	1.76 (0.96–3.38)		1.33 (0.62–2.89)	
CA 19-9 (U/ml)		1.00 (1.00–1.00)	0.006	1.00 (1.00–1.00)	0.260
CEA (ng/ml)		1.02 (1.00–1.03)	0.011	1.00 (0.97–1.03)	0.971
CE (HU)		0.98 (0.96–0.99)	<0.001	-	-
ECV fraction (%)		0.97 (0.95–0.99)	0.001	0.97 (0.95–0.99)	0.012

CA carbohydrate antigen, *CEA* carcinoembryonic antigen, *CE* contrast enhancement, *ECV* extracellular volume

Numbers in parentheses represent 95% confidence intervals

Statistically significant results from Cox proportional hazard model

estimate of tumour ECV fraction helped predict outcomes of patients with unresectable pancreatic adenocarcinoma treated with chemotherapy. Our study makes a strong case for wider application of the equilibrium techniques beyond its traditional use for assessment of myocardial and liver fibrosis and amyloidosis. The good inter-observer agreement regarding evaluation of ECV fraction within tumour underlines the potential for its application to malignant tumours.

Tumour vascularity is a key determinant of the biological aggressiveness of a neoplasm and appears to be associated with unfavourable outcomes in patients with pancreatic adenocarcinoma [12, 25]. Hypoxic regions with acidic environment caused by poor tumour blood supply are known to be resistant to chemotherapy [26]. CT is a widely accepted technique for detection, diagnosis, initial staging and treatment surveillance of pancreatic adenocarcinoma [27, 28]. Contrast-enhanced CT has been used for assessment of tumour vascularity in the context of several tumours. Pancreatic ductal adenocarcinomas tend to exhibit a hypovascular pattern during the arterial to portal venous phase. However, some pancreatic adenocarcinomas do not show hypovascular findings [29, 30]. Kim et al [30] reported that isoattenuation of pancreatic adenocarcinoma during the pancreatic parenchymal and portal venous phases of enhanced CT was associated with better survival outcomes after curative-intent surgery as compared to those associated with usual hypoattenuation. In a study by Fukukura et al [31], pancreatic adenocarcinoma that showed lower CE during all phases (including the pancreatic parenchymal, portal venous and delayed phases after contrast material administration) were associated with significantly shorter survival as compared to those that showed higher CE; the association held true both for patients who underwent curative-intent surgery and those who did not. In our study, patients with higher tumour CE survived longer after chemotherapy than those with lower tumour CE during the equilibrium phase, which is consistent with the results of the previous study [31]. However, CE within the tumour depends not only on tumour vascularity (including blood flow, blood volume, permeability and extracellular extravascular components), but also on the CT scanning protocol and patient characteristics [31].

Tumour aggressiveness and response to therapy are influenced by the extravascular extracellular volume fraction of the malignant tissue [18]. Dynamic contrast-enhanced CT and MR imaging have been employed to quantify the extravascular extracellular volume fraction and to predict the response to chemotherapy or prognosis in patients with various cancers such as orpharyngeal or hypopharyngeal cancer, rectal cancer, ovarian cancer and osteosarcoma [6–9]. ECV fraction, comprising intravascular space and extravascular extracellular volume fractions, can be quantified with equilibrium contrast-enhanced CT or MR imaging, which can be easily integrated into routine examination. In a study by Bandula et al [23], estimates of the extravascular extracellular volume fraction in the liver and skeletal muscle determined by dynamic contrast-enhanced MR imaging were consistent with ECV

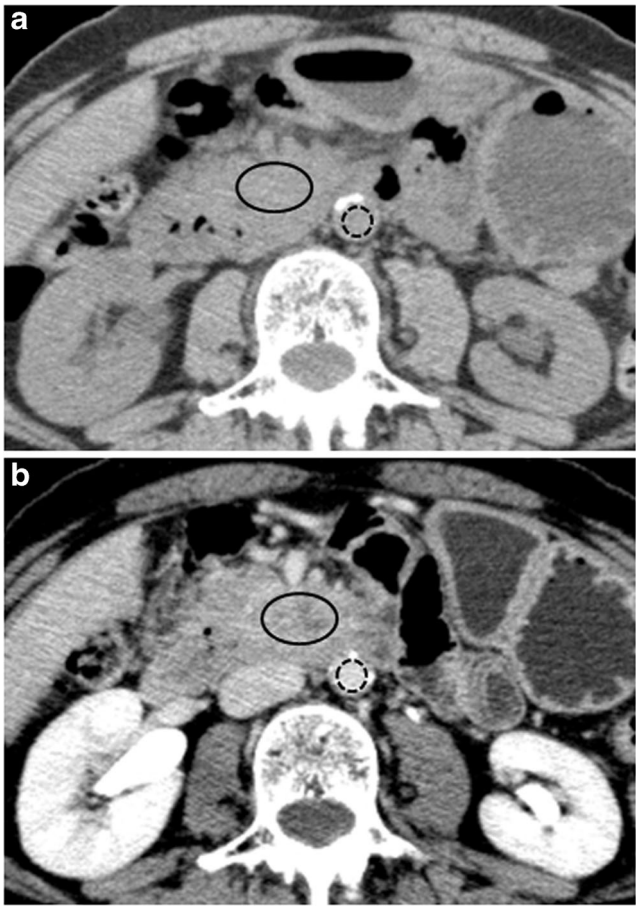

Fig. 2 A 68-year-old woman with pancreatic adenocarcinoma (TNM stage IV) who survived for 21.9 months after chemotherapy. Axial unenhanced (**a**) and equilibrium phase contrast-enhanced CT (**b**) show regions of interest placed on a tumour measuring 36 mm in diameter (black circles) in the pancreas head and the aorta (black dotted circles). Tumour contrast enhancement and extracellular volume fraction were 61.8 HU and 38.8%, respectively

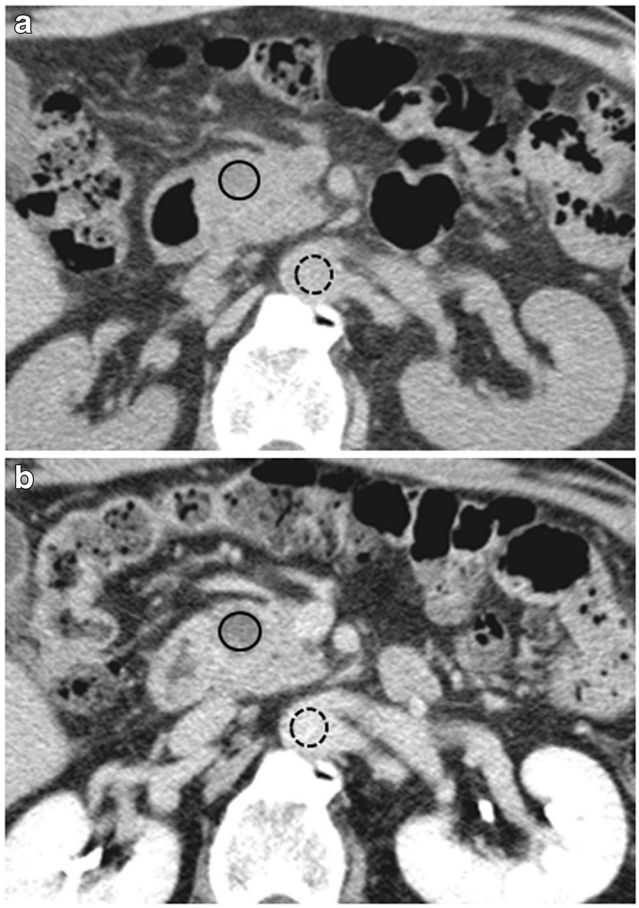

Fig. 3 A 62-year-old man with pancreatic adenocarcinoma (TNM stage IV) who died 7.4 months after chemotherapy. Axial unenhanced (**a**) and equilibrium phase contrast-enhanced CT (**b**) show regions of interest placed on a tumour measuring 20 mm in diameter (black circles) and the aorta (black dotted circles). Tumour contrast enhancement and extracellular volume fraction were 14.5 HU and 14.7%, respectively

fraction determined by equilibrium MR imaging. We employed equilibrium CT to determine tumour ECV fraction, which was estimated as the ratio of enhancement of pancreatic adenocarcinoma to that of the aorta multiplied by the difference of 1 minus the haematocrit value [16, 17]. The measurement of ECV fraction using CT has been previously validated in that equilibrium CT was as reliable as equilibrium MR imaging for measuring ECV fraction and that they correlated well with the fibrosis burden of the myocardium [14]. CT offers several advantages over MR imaging; these include wider availability of equipment, higher spatial resolution and a simple linear relationship between attenuation and iodine concentration in contrast to the nonlinear effect of hydrogen on relaxivity following administration of gadolinium.

In our study, patients with higher tumour ECV fraction had a better prognosis than those with lower tumour ECV fraction. Tumour ECV fraction was an independent predictor of survival in patients with unresectable pancreatic adenocarcinoma treated with chemotherapy. Moreover, we determined the optimal cut-off values of tumour ECV fraction for predicting 1-year survivor. Patients with higher tumour ECV fraction survived longer than those with lower tumour ECV fraction, when stratified by the cut-off value (28.0%). Our results suggested that tumour ECV fraction may be useful for predicting 1-year survivor after chemotherapy, with a sensitivity of 75.0% and specificity of 77.1%. Unravelling the mechanisms that underlie this association represents a challenge. At this point, we can only speculate on the possible mechanisms. Tumours with higher extravascular extracellular volume fraction have been shown to exhibit a higher uptake of anticancer drugs as compared to that in tumours with lower extravascular extracellular volume fraction [32–34]. Pancreatic adenocarcinoma is known to be a hypovascular tumour, which is reflected by the small blood volume values in the tumour. Thus, we presume that the contribution of the intravascular space to the total attenuation in pancreatic

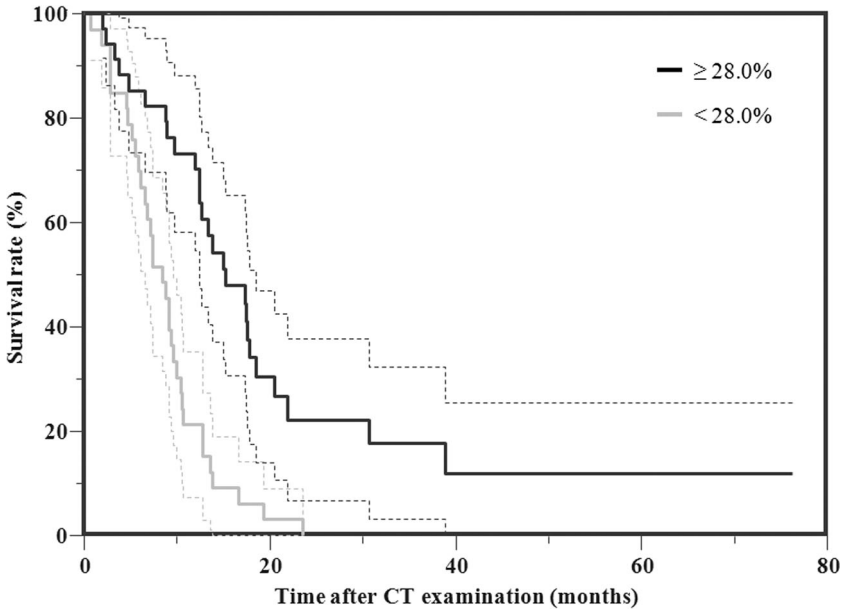

Fig. 4 Kaplan–Meier survival curves for patients with pancreatic adenocarcinomas disaggregated by tumour extracellular volume fraction (< 28.0% vs. ≥ 28.0%) determined on equilibrium contrast-enhanced MDCT. Patients with tumour extracellular volume fractions of ≥ 28.0% (black solid line) survived longer than those with tumour extracellular volume fractions of < 28.0% (grey solid line) (P < 0.001, log-rank test). Dotted lines represent 95% confidence intervals

adenocarcinoma can be ignored. It is likely that under these circumstances, ECV fraction value plays an important role in the delivery of chemotherapeutic agents to pancreatic adenocarcinoma as does extravascular extracellular volume fraction. However, a direct comparison of ECV fraction from equilibrium imaging and the extravascular extracellular volume fraction from dynamic contrast-enhanced imaging has not yet been made in the context of this tumour. Moreover, in this study cohort, histopathological examination of the intratumoral extracellular component could not be performed because all patients were unresectable due to the advanced stage of the disease and histopathological examination of biopsy specimens tends to be affected by sample variability. Therefore, this issue requires further investigation.

Some limitations of this study must be considered. First, the sample size of patients was small and the study was retrospective. Second, we determined TNM stage according to the UICC classification of pancreatic adenocarcinoma based on preoperative CT, MR imaging and/or FDG-PET. However, the accuracy of preoperative assessment of pancreatic adenocarcinoma based on CT, MR imaging or FDG-PET is likely to be compromised by the presence of scattered local extension, lymph node metastases, small hepatic metastases and peritoneal seeding. The possibility that we may have underestimated the TNM stage of pancreatic adenocarcinoma cannot be ruled out. Third, we measured tumour ECV fraction using 3-min delayed-phase CT. Three minutes may not be sufficient to calculate ECV fraction because 10-min or longer delayed phases were used previously in the literature [14–17]. However, the minimum scan delay for reliable estimation of the ECV fraction has not been well defined. Yoon et al [35] reported that the equilibrium phase at 3 min is a good compromise between clinical workflow and technical success for the estimation of ECV fraction that may have the potential to detect significant hepatic fibrosis. This issue requires further investigation.

In conclusion, we examined prognostic factors in patients with unresectable pancreatic adenocarcinomas treated with chemotherapy. Pancreatic adenocarcinomas with lower ECV fraction on equilibrium contrast-enhanced MDCT were associated with reduced patient survival after chemotherapy. Thus, pretreatment ECV fraction determined by equilibrium contrast-enhanced MDCT may predict overall survival in patients with pancreatic adenocarcinoma treated with chemotherapy and may be helpful in the surveillance and management of patients with unresectable pancreatic adenocarcinoma.

Acknowledgements We thank Dr. Chihaya Koriyama for help with statistical analysis.

Funding The authors state that this work has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Yoshihiko Fukukura MD, PhD.

Conflict of interest The authors of this article declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

References

1. Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E (2014) European cancer mortality predictions for the year 2014. Ann Oncol 25:1650–1656
2. Willett CG, Czito BG, Bendell JC, Ryan DP (2005) Locally advanced pancreatic cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 23: 4538–4544
3. Matsuno S, Egawa S, Fukuyama S et al (2004) Pancreatic Cancer Registry in Japan: 20 years of experience. Pancreas 28:219–230
4. Ozaka M, Matsumura Y, Ishii H et al (2012) Randomized phase II study of gemcitabine and S-1 combination versus gemcitabine alone in the treatment of unresectable advanced pancreatic cancer (Japan Clinical Cancer Research Organization PC-01 study). Cancer Chemother Pharmacol 69:1197–1204
5. Li Q, Yan H, Liu W, Zhen H, Yang Y, Cao B (2014) Efficacy and safety of gemcitabine-fluorouracil combination therapy in the management of advanced pancreatic cancer: a meta-analysis of randomized controlled trials. PLoS One 9:e104346
6. Tong T, Sun Y, Gollub MJ et al (2015) Dynamic contrast-enhanced MRI: Use in predicting pathological complete response to neoadjuvant chemoradiation in locally advanced rectal cancer. J Magn Reson Imaging 42:673–680
7. Ng SH, Lin CY, Chan SC et al (2014) Clinical utility of multimodality imaging with dynamic contrast-enhanced MRI, diffusion-weighted MRI, and 18F-FDG PET/CT for the prediction of neck control in oropharyngeal or hypopharyngeal squamous cell carcinoma treated with chemoradiation. PLoS One 9:e115933
8. Guo J, Reddick WE, Glass JO et al (2012) Dynamic contrast-enhanced magnetic resonance imaging as a prognostic factor in predicting event-free and overall survival in pediatric patients with osteosarcoma. Cancer 118:3776–3785
9. Sala E, Kataoka MY, Priest AN et al (2012) Advanced ovarian cancer: multiparametric MR imaging demonstrates response- and metastasis-specific effects. Radiology 263:149–159
10. Park MS, Klotz E, Kim MJ et al (2009) Perfusion CT: noninvasive surrogate marker for stratification of pancreatic cancer response to concurrent chemo- and radiation therapy. Radiology 250:110–117
11. Bali MA, Metens T, Denolin V et al (2011) Tumoral and nontumoral pancreas: correlation between quantitative dynamic contrast-enhanced MR imaging and histopathologic parameters. Radiology 261:456–466
12. Couvelard A, O'Toole D, Leek R et al (2005) Expression of hypoxia-inducible factors is correlated with the presence of a fibrotic focus and angiogenesis in pancreatic ductal adenocarcinomas. Histopathology 46:668–676
13. Flett AS, Hayward MP, Ashworth MT et al (2010) Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. Circulation 122:138–144
14. Bandula S, White SK, Flett AS et al (2013) Measurement of myocardial extracellular volume fraction by using equilibrium contrast-enhanced CT: validation against histologic findings. Radiology 269:396–403
15. Bandula S, Punwani S, Rosenberg WM et al (2015) Equilibrium contrast-enhanced CT imaging to evaluate hepatic fibrosis: initial validation by comparison with histopathologic sampling. Radiology 275:136–143
16. Zissen MH, Wang ZJ, Yee J, Aslam R, Monto A, Yeh BM (2013) Contrast-enhanced CT quantification of the hepatic fractional extracellular space: correlation with diffuse liver disease severity. AJR Am J Roentgenol 201:1204–1210
17. Varenika V, Fu Y, Maher JJ et al (2013) Hepatic fibrosis: evaluation with semiquantitative contrast-enhanced CT. Radiology 266:151–158
18. Benjaminsen IC, Brurberg KG, Ruud EB, Rofstad EK (2008) Assessment of extravascular extracellular space fraction in human melanoma xenografts by DCE-MRI and kinetic modeling. Magn Reson Imaging 26:160–170
19. Prokesch RW, Chow LC, Beaulieu CF et al (2002) Local staging of pancreatic carcinoma with multi-detector row CT: use of curved planar reformations initial experience. Radiology 225: 759–765
20. Roche CJ, Hughes ML, Garvey CJ et al (2003) CT and pathologic assessment of prospective nodal staging in patients with ductal adenocarcinoma of the head of the pancreas. AJR Am J Roentgenol 180:475–480
21. Bartlett JW, Frost C (2008) Reliability, repeatability and reproducibility: analysis of measurement errors in continuous variables. Ultrasound Obstet Gynecol 31:466–475
22. Yeung J, Sivarajan S, Treibel TA et al (2017) Measurement of liver and spleen interstitial volume in patients with systemic amyloid light-chain amyloidosis using equilibrium contrast CT. Abdom Radiol (NY) 42:2646–2651
23. Bandula S, Banypersad SM, Sado D et al (2013) Measurement of tissue interstitial volume in healthy patients and those with amyloidosis with equilibrium contrast-enhanced MR imaging. Radiology 268:858–864
24. Banypersad SM, Sado DM, Flett AS et al (2013) Quantification of myocardial extracellular volume fraction in systemic AL amyloidosis: an equilibrium contrast cardiovascular magnetic resonance study. Circ Cardiovasc imaging 6:34–39
25. Komar G, Kauhanen S, Liukko K et al (2009) Decreased blood flow with increased metabolic activity: a novel sign of pancreatic tumor aggressiveness. Clin Cancer Res 15:5511–5517
26. Tatum JL, Kelloff GJ, Gillies RJ et al (2006) Hypoxia: importance in tumor biology, noninvasive measurement by imaging, and value of its measurement in the management of cancer therapy. Int J Radiat Biol 82:699–757
27. Koelblinger C, Ba-Ssalamah A, Goetzinger P et al (2011) Gadobenate dimeglumine-enhanced 3.0-T MR imaging versus multiphasic 64-detector row CT: prospective evaluation in patients suspected of having pancreatic cancer. Radiology 259: 757–766
28. Schima W, Ba-Ssalamah A, Kolblinger C, Kulinna-Cosentini C, Puespoek A, Gotzinger P (2007) Pancreatic adenocarcinoma. Eur Radiol 17:638–649
29. Yoon SH, Lee JM, Cho JY et al (2011) Small (</= 20 mm) pancreatic adenocarcinomas: analysis of enhancement patterns and secondary signs with multiphasic multidetector CT. Radiology 259: 442–452
30. Kim JH, Park SH, Yu ES et al (2010) Visually isoattenuating pancreatic adenocarcinoma at dynamic-enhanced CT: frequency, clinical and pathologic characteristics, and diagnosis at imaging examinations. Radiology 257:87–96
31. Fukukura Y, Takumi K, Higashi M et al (2014) Contrast-enhanced CT and diffusion-weighted MR imaging: performance as a prognostic factor in patients with pancreatic ductal adenocarcinoma. Eur J Radiol 83:612–619

32. Krol A, Maresca J, Dewhirst MW, Yuan F (1999) Available volume fraction of macromolecules in the extravascular space of a fibrosarcoma: implications for drug delivery. Cancer Res 59:4136–4141
33. Jain RK (1996) Delivery of molecular medicine to solid tumors. Science 271:1079–1080
34. Jain RK (1987) Transport of molecules in the tumor interstitium: a review. Cancer Res 47:3039–3051
35. Yoon JH, Lee JM, Klotz E et al (2015) Estimation of hepatic extracellular volume fraction using multiphasic liver computed tomography for hepatic fibrosis grading. Invest Radiol 50:290–296