Individually optimized contrast-enhanced 4D-CT for radiotherapy simulation in pancreatic ductal adenocarcinoma

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Purpose: To develop an individually optimized contrast-enhanced (CE) 4D-computed tomography (CT) for radiotherapy simulation in pancreatic ductal adenocarcinomas (PDA).

Methods: Ten PDA patients were enrolled. Each underwent three CT scans: a 4D-CT immediately following a CE 3D-CT and an individually optimized CE 4D-CT using test injection. Three physicians contoured the tumor and pancreatic tissues. Image quality scores, tumor volume, motion, tumor-to-pancreas contrast, and contrast-to-noise ratio (CNR) were compared in the three CTs. Interobserver variations were also evaluated in contouring the tumor using simultaneous truth and performance level estimation.

Results: Average image quality scores for CE 3D-CT and CE 4D-CT were comparable (4.0 and 3.8, respectively; $P = 0.082$), and both were significantly better than that for 4D-CT (2.6, $P < 0.001$). Tumor-to-pancreas contrast results were comparable in CE 3D-CT and CE 4D-CT (15.5 and 16.7 Hounsfield units (HU), respectively; $P = 0.21$), and the latter was significantly higher than in 4D-CT (9.2 HU, $P = 0.001$). Image noise in CE 3D-CT (12.5 HU) was significantly lower than in CE 4D-CT (22.1 HU, $P = 0.013$) and 4D-CT (19.4 HU, $P = 0.009$). CNRs were comparable in CE 3D-CT and CE 4D-CT (1.4 and 0.8, respectively; $P = 0.42$), and both were significantly better in 4D-CT (0.6, $P = 0.008$ and 0.014). Mean tumor volumes were significantly smaller in CE 3D-CT (29.8 cm³, $P = 0.03$) and CE 4D-CT (22.8 cm³, $P = 0.01$) than in 4D-CT (42.0 cm³). Mean tumor motion was comparable in 4D-CT and CE 4D-CT (7.2 and 6.2 mm, $P = 0.17$). Interobserver variations were comparable in CE 3D-CT and CE 4D-CT (Jaccard index 66.0% and 61.9%, respectively) and were worse for 4D-CT (55.6%) than CE 3D-CT.

Conclusions: CE 4D-CT demonstrated characteristics comparable to CE 3D-CT, with high potential for simultaneously delineating the tumor and quantifying tumor motion with a single scan.

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Key words: contrast enhancement, 4D-CT, pancreatic ductal adenocarcinoma, radiotherapy simulation

1. INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death in the United States.¹ Pancreatic ductal adenocarcinomas (PDA) comprise about 90% of all pancreatic cancers.² At the time of diagnosis, more than 80% of patients were present with unresectable locally advanced or metastatic disease for which chemotherapy and/or radiotherapy (RT) are commonly prescribed.² Modern RT is capable of delivering a precisely conformal dose to the target volumes. PDA is relatively radioresistant, and neighboring organs are highly sensitive to radiation;^{3,4} therefore, it is critical to accurately and precisely delineate target volumes for RT planning. There are two major difficulties in this task. First, the tumors have density and computed tomography (CT) numbers [Hounsfield units (HU)] similar to that of surrounding normal pancreatic tissues. Second, the tumors may move a large amount, up to 1–2 cm,^{5–7} secondary to respiration. In current RT simulation, a contrast-enhanced (CE) 3D-CT is acquired along with a respiratory-correlated 4D-CT to address these difficulties.

Intravenously (IV) administered contrast medium is regularly used to enhance tumor-to-pancreas contrast in CT. Pancreatic cancers are relatively hypovascular (containing fewer blood vessels than normal pancreatic tissues) and thus are hypodense on CE CT.⁸ Unenhanced 4D-CT has been widely used to quantify and compensate tumor respiratory motion for RT planning. However, most abdominal tumors (liver, pancreas, etc.) cannot be readily visualized on CT images without contrast enhancement. Therefore, it is desirable to incorporate contrast enhancement into 4D-CT so that the tumor is visualized, while its motion is quantified with a single CE 4D-CT scan.

Because of safety concerns associated with increasing the contrast dose to allow for the much longer acquisition time of 4D-CT (60–75 s), it is preferable to synchronize the contrast injection with the 4D-CT scan so that peak contrast enhancement coincides with the time point at which the tumor region is scanned. In previous studies, the delay time between injection of contrast and the start of a CE 4D-CT scan was set to acquire the central part of the pancreas at 50 s from injection.^{9–11} This fixed-delay method assumes the same injection duration and disregards wide variations in contrast arrival time. It is therefore not optimal for individual patients.

In this study, a CE 4D-CT technique, which utilized a test injection to estimate the time of peak enhancement and synchronized the contrast injection with the 4D-CT scan for individual patients, was developed and validated. The proposed CE 4D-CT was compared to CE 3D-CT and 4D-CT to evaluate the ability of each technique to visualize the tumor.

2. METHODS AND MATERIALS

2.A. Patient data

This prospective study was approved by our institutional review board. Ten PDA patients were enrolled and underwent three CT scans under quiet breathing: a CE 3D-CT followed immediately by a 4D-CT and a CE 4D-CT 1–2 weeks later

immediately prior to the start of planned RT. The pair of CE 3D-CT and 4D-CT is our clinical standard care for RT simulation, and the CE 4D-CT was for research only. A patient follow-up renal function exam was performed 2–5 days after the CE 4D-CT to evaluate for any acute postcontrast kidney injury.

All CT scans were acquired with a Philips Big Bore Brilliance 16-slice CT scanner (Philips Healthcare; Andover, MA). A real-time position management (RPM) system (Varian Medical Systems; Palo Alto, CA) was used to track patients' respiratory motion for 4D-CTs. A Medrad Stellant CT Injector was used for IV contrast injections with Omnipaque (iohexol) 300 mgI/ml (GE Healthcare; Milwaukee, WI) as the contrast medium. CT scan parameters were as follows: 120 kVp, 400 mAs/slice for CE 3D-CT and 1000 mAs/slice for both 4D-CTs, 16 × 1.5-mm collimation, 3-mm slice thickness, and approximately 1 × 1 × 3-mm resolution. The radiation exposure was 26 mGy for the CE 3D-CT and 66 mGy for the 4D-CTs. The typical pitch and gantry rotation time were 0.813 and 0.75 s for CE 3D-CT, and 0.071 and 0.5 s for both 4D-CTs.

2.A.1. CE 3D-CT

After setting the patient up on the CT table with immobilization devices and making sure that his or her spine was straight, a CT localizer radiograph scan was acquired to determine the level of interest (LOI) at about the 2/3 craniocaudal level of the pancreatic region, which spans from the T12 to L2 vertebral body levels (Fig. 1).^{9,12,13} A bolus tracking technique was used for contrast timing. In brief, a single axial image (the locator) was acquired at the LOI, and a region of interest (ROI) was defined in the aorta. Ninety milliliters of contrast was injected at a rate from 1.5 to 3.0 ml/s while a series of low-dose axial scans (the tracker) was acquired every 1.5 s at the LOI. The CT software tracked the mean contrast enhancement of the ROI in the tracker images, and when a threshold of 150 HU was reached, the tracker scan was stopped and the CE 3D-CT helical scan was started.

2.A.2. 4D-CT

Immediately following the CE 3D-CT acquisition, a helical 4D-CT was acquired with the RPM system. The 4D-CT scan was reconstructed at ten breathing phases (0%–90% phases), where 0% phase was the end of inhalation and 50% phase was the end of exhalation.

2.A.3. CE 4D-CT

One to two weeks after the CE 3D-CT and 4D-CT session and immediately prior to the start of planned radiotherapy, a CE 4D-CT was acquired with the same immobilization device, contrast injection rate, and scan parameters as the CE 3D-CT and 4D-CT. The only difference was that a test injection technique was used for contrast timing. In brief, a 10-ml test-bolus contrast was injected while a series of low-dose axial scans was simultaneously acquired at the LOI. Contrast enhancement of the aorta ROI was charted as a function of elapsed time with the CT console software. The

FIG. 1. Delay time (T_{delay}) was optimized between start of 4D-CT acquisition and start of contrast injection; (a) and (e) are the starting and ending positions of the 4D-CT, respectively; range (b)–(d) is the pancreatic region; (c) level of interest at 2/3 of the pancreatic region.

time to peak test-bolus contrast enhancement (the contrast arrival time T_{arr}) was recorded and then used to estimate the peak enhancement time T_{peak} for a full-bolus injection of 140 ml contrast, which was injected at a rate from 1.5 to 3.0 ml/s for the CE 4D-CT acquisition using the equation

$$T_{\text{peak}} = T_{\text{ID}} + 15 \text{ s} + (T_{\text{arr}} - 20 \text{ s}),$$

where T_{ID} was the contrast injection duration, 15 s was the typical contrast transit time from the injection site to pancreas, and 20 s was the typical contrast arrival time for a standard patient (60 kg) with normal circulation.^{14–17} Therefore, $(T_{\text{arr}} - 20 \text{ s})$ represented the T_{arr} deviation of a specific patient from the standard patient.

Finally, the contrast injection delay time T_{delay} was calculated using the equation

$$T_{\text{delay}} = T_0 - T_{\text{peak}} = L_0/V - T_{\text{peak}},$$

where L_0 was the length between the scan start position and the LOI, and V was the table speed expressed as $V = \text{Collimation} \times \text{pitch} / \text{Rotation time}$ (typical $V = 3.408 \text{ mm/s}$) (Fig. 1). With T_{delay} , the CE 4D-CT acquisition and contrast enhancement were synchronized: the LOI and the pancreatic region were scanned at peak contrast enhancement (Fig. 1).

2.B. Comparison of CE 3D-CT, 4D-CT, and CE 4D-CT

Three CTs, CE 3D-CT, 4D-CT, and CE 4D-CT, were compared qualitatively and quantitatively. For both 4D-CTs,

the images at 50% phase (end of exhalation, generally most stable) were selected for comparison. The Wilcoxon signed rank test was used to evaluate differences between the three CTs. The following visual evaluation and manual contouring were performed using an open source software 3D Slicer (<http://www.slicer.org>)¹⁸ with the same window/level (350/40 HU) display settings for all images.

2.B.1. Qualitative image quality scores

A radiologist (RA1) and 2 radiation oncologists (RO1 and RO2) who specialized in gastrointestinal/pancreas disease scored the three CT images by a visual evaluation of the following: (1) general image quality, in terms of anatomic details, motion artifacts, beam hardening, and enhancement of pancreatic tissues and tumor; and (2) regional vessel definition, in terms of their characterization, detail, and enhancement. Regional vessels included the abdominal aorta, superior mesenteric artery, superior mesenteric vein, portal vein, splenic vein, hepatic artery, and celiac axis. Scores were assigned as follows: 1 = very poor; 2 = unsatisfactory; 3 = sufficient; 4 = good; and 5 = excellent.

2.B.2. Tumor volume and tumor motion

All three physicians contoured the tumor [gross tumor volume (GTV)] (T) and normal pancreatic tissues (P) on the three CT images (Fig. 2). GTV included the primary tumor

FIG. 2. Tumor (red) and normal pancreatic tissues (blue) contours on (a) CE 3D-CT, (b) 4D-CT, and (c) CE 4D-CT. (See color online version.)

and any lymph nodes enlarged over 1 cm. Contouring on each of the three CT images for each patient was separated by at least one week. In addition, one physician contoured the GTVs on four phases (0%, 20%, 50%, and 70%) of both 4D-CT and CE 4D-CT for motion analysis.

An internal gross target volume (IGTV₄) was defined as the union of the four GTVs, and tumor motion was measured as the centroid distance between GTV_{0%} and GTV_{50%} in all three directions [left–right (LR), anterior–posterior (AP), and superior–inferior (SI)] and in 3D.

In accordance with institutional guidelines,¹² CTV was created by expanding the GTV by 0.7 cm. ITV was created by expanding CTV by internal margins (IM) to account for organ motion which was estimated by 4D-CT. A setup margin (SM) of 5 mm (isotropic) was added to the ITV to generate a PTV. If 4D-CT is unavailable or for the CE 3D-CT, a margin of 1.5 cm was added in cranial-caudal directions and 0.5 cm in other directions to generate PTV by expanding CTV.

2.B.3. Contrast enhancement, tumor-to-pancreas contrast, and contrast-to-noise ratio (CNR)

The following image analysis was performed using the Insight Segmentation and Registration Toolkit (ITK, National Library of Medicine; Bethesda, MD).¹⁹ Extremely high-density objects (e.g., stents) were automatically identified by thresholding ($I_t = I > 500$ HU) from a CT image I followed by a 2D morphologic dilation with a circular-shaped structuring element $\text{Dilate}(I_t, r)$, where I_t was the thresholded image and r was the radius of the structuring element. Since the resulting volumes approximated the high-density objects, r was experimentally selected as 2 mm. The contrast enhancement of the tumor and pancreatic tissues was calculated as the mean CT number within each volume but excluding the high-density objects.

The tumor-to-pancreas contrast (C) and contrast-to-noise ratios were evaluated in regions adjacent to the tumor–pancreas boundary. As illustrated in Fig. 3, these regions (P' and T') were obtained by $P' = P \cap \text{Dilate}(T, r)$ and $T' = T \cap \text{Dilate}(P, r)$. In this case, we chose $r = 5$ mm; thus, C and CNR were computed in these 5-mm-wide regions adjacent

FIG. 3. Regions adjacent to the tumor–pancreas boundary were selected by 2D morphologic dilation with a circular structuring element ($r = 5$ mm), $P' = P \cap \text{Dilate}(T, r)$ and $T' = T \cap \text{Dilate}(P, r)$; red is tumor (T), blue is pancreas (P), and deep color is the selected region. (See color online version.)

to the tumor–pancreas boundary using

$$C = |\mu(P') - \mu(T')|,$$

where $\mu(P')$ and $\mu(T')$ were the mean CT numbers of P' and T' , respectively; and

$$\text{CNR} = \frac{C}{\sigma_f},$$

where σ_f was the image noise level, which was measured as the standard deviation of the CT numbers within an ROI (5-mm-radius circle) manually defined in a homogeneous region of abdominal subcutaneous fat. For comparison to other studies, the tumor-to-pancreas contrast was also evaluated in the entire tumor and pancreas volumes using

$$C_{\text{entire volumes}} = |\mu(P) - \mu(T)|.$$

2.B.4. Interobserver variation

Interobserver variation was investigated in contouring the GTV on the three CT images. Simultaneous truth and performance level estimation (STAPLE) was applied to quantify interobserver variation.^{20,21} A group consensus contour was generated based on the three physicians' contours by the maximum-likelihood estimate from the STAPLE. Agreement between each individual physician's contour and the group consensus contour was measured with sensitivity, specificity, and Jaccard index as

$$\text{Sensitivity} = \frac{S \cap G}{G},$$

$$\text{Specificity} = \frac{\bar{S} \cap \bar{G}}{\bar{G}},$$

$$\text{Jaccard index} = \frac{S \cap G}{S \cup G},$$

where S was the individual contour, G was the group consensus contour, and $\bar{S}$ and $\bar{G}$ denoted the space outside S and G , respectively.²¹ In order to balance the weights of sensitivity and specificity in the estimation, a small region enclosing all individual contours was selected with forced volume of the space outside G to be roughly equivalent to G ($G \cong \bar{G}$). Higher values of these STAPLE measures (ranges: [0,1]) indicate higher agreement among physicians' contours and thus smaller interobserver variation.

3. RESULTS

All patients had normal renal function at the follow-up test.

3.A. Image quality scores

Image quality scores averaged for all three physicians are shown in Table I. The overall average scores of CE 3D-CT and CE 4D-CT were comparable (4.0 and 3.8, respectively; $P = 0.082$) and both were significantly better than that of 4D-CT (2.6, $P < 0.001$). CE 3D-CT showed better scores in anatomic details and beam hardening than CE 4D-CT. The other scores were comparable. Both CE 3D-CT and CE 4D-CT showed better scores in anatomic details, enhancement of

TABLE I. Comparison of image quality scores for CE 3D-CT, 4D-CT, and CE 4D-CT. Scores ranged from 1 to 5, with 1 being “very poor” and 5 being “excellent.”

		CE 3D-CT	4D-CT	CE 4D-CT
General image quality	Anatomic details	4.1 ± 0.8	2.5 ± 0.6	3.6 ± 0.8
	Motion artifacts	3.9 ± 1.0	3.4 ± 0.9	3.7 ± 0.8
	Beam hardening	4.2 ± 0.8	3.3 ± 0.9	3.5 ± 0.8
	Enhancement of pancreatic tissue and tumor	3.2 ± 1.0	1.7 ± 0.9	3.3 ± 1.0
Average of regional vessel definition		4.2 ± 1.1	2.7 ± 1.5	4.1 ± 1.3
Overall average		4.0 ± 0.5	2.6 ± 0.5	3.8 ± 0.4
Signed rank test (<i>P</i>)		<0.001 ^a vs 4D-CT	<0.001 ^a vs CE 4D-CT	0.082 vs CE 3D-CT

^aSignificant at 0.05.

pancreatic tissues and tumor, and regional vessel definition than 4D-CT. RA1 gave lower scores (3.4, 2.0, and 3.2 for CE 3D-CT, 4D-CT, and CE 4D-CT, respectively) than both RO1 (4.1, 2.6, and 3.8) and RO2 (4.4, 3.1, and 4.3). However, the trends of their scores were similar.

3.B. Tumor volume and tumor motion

The average tumor volumes (GTV_{50%}, IGTV₄, and PTV) were all significantly smaller in CE 4D-CT than in 4D-CT (Table II). The average GTV_{50%} and PTV in CE 4D-CT (22.8 and 145.4 cm³) were comparable to the average GTV and PTV in CE 3D-CT (29.8 and 160.4 cm³), and they were significantly smaller than the average GTV_{50%} and PTV in 4D-CT (42.0 and 204.1 cm³).

The average amplitudes, maximum amplitudes, and breathing rates obtained from the RPM signal were all comparable between 4D-CT and CE 4D-CT (Table III). The average GTV motions in all three directions and in 3D (7.2 and 6.2 mm, respectively; *P* = 0.17) were comparable in 4D-CT and CE 4D-CT (Table III), with the greatest motion in the SI direction. The average OAR motions were also comparable in 4D-CT and CE 4D-CT (right and left kidneys listed in Table III).

3.C. Contrast enhancement, tumor-to-pancreas contrast, and CNR

As shown in Table IV, the average CT numbers (absolute contrast enhancement) of both tumor and normal pancreatic tissues in CE 4D-CT (76.3 and 75.5 HU, respectively) were significantly higher than those in CE 3D-CT (53.0 and 49.2 HU, respectively) and 4D-CT (58.9 and 44.6 HU, respectively). Tumor-to-pancreas contrasts evaluated in the boundary regions in CE 3D-CT and CE 4D-CT were

comparable (15.5 and 16.7 HU, respectively; *P* = 0.21), and the latter was significantly higher than that in 4D-CT (9.2 HU, *P* = 0.001). Tumor-to-pancreas contrasts evaluated in the entire tumor and pancreas volumes were comparable in all three images (15.8, 15.1, and 17.6 HU). The image noise of CE 3D-CT (12.5 HU) was significantly lower than that of 4D-CT (19.4 HU) and CE 4D-CT (22.1 HU), as shown also in Fig. 2. However, tumor CNR was not significantly different between CE 3D-CT and CE 4D-CT (1.4 and 0.8, respectively; *P* = 0.42). Tumor CNRs in CE 3D-CT and CE 4D-CT were significantly better than that in 4D-CT (0.6; *P* = 0.008 and 0.014, respectively).

3.D. Interobserver variation in contouring the GTV

The sensitivity, specificity, and Jaccard indexes between the individual contours and the group consensus contours are listed in Table V. On average, interobserver variation was smaller in CE 3D-CT (sensitivity 78.0%, specificity 73.7%, and Jaccard index 66.0%) and CE 4D-CT (72.2%, 72.5%, and 61.9%) than in 4D-CT (66.5%, 72.7%, and 55.6%). Differences between CE 3D-CT and CE 4D-CT were not statistically significant. Physician RA1 had lower sensitivity and higher specificity, indicating that his contours were generally smaller than those of the others. Overall, average Jaccard index scores were lower than 70%, indicating a considerable interobserver variation in contouring the GTVs on all three CT images.

3.E. Comparison between the fixed-delay CE 4D-CT and the optimized-delay CE 4D-CT

Table VI compares the reported results of the fixed-delay CE 4D-CT against the optimized-delay CE 4D-CT. It should

TABLE II. Comparison of tumor volumes in CE 3D-CT, 4D-CT, and CE 4D-CT.

		CE 3D-CT	4D-CT	CE 4D-CT
Average volume (cm ³)	GTV/GTV ₅₀	29.8 ± 16.6	42.0 ± 35.1	22.8 ± 18.9
	IGTV ₄	N/A	56.0 ± 38.1	32.8 ± 26.4
	PTV	160.4 ± 59.0	204.1 ± 94.0	145.4 ± 70.2
Signed rank test (<i>P</i>)		0.03 ^a vs 4D-CT	0.01 ^a vs CE 4D-CT	0.46 vs CE 3D-CT

^aSignificant at 0.05.

TABLE III. Comparison of RPM signals and tumor motions in 4D-CT and CE 4D-CT.

		4D-CT	CE 4D-CT	<i>P</i>
RPM signal	Average (cm)	0.8 ± 0.4	0.8 ± 0.3	0.51
	Maximum (cm)	1.3 ± 0.5	1.2 ± 0.5	0.39
	Breath per min	15.0 ± 2.5	16.3 ± 2.5	0.15
GTV motion (mm)	LR	2.3 ± 1.7	1.1 ± 0.5	0.14
	AP	2.8 ± 1.6	2.6 ± 1.6	0.80
	SI	6.0 ± 1.7	5.4 ± 1.6	0.39
	3D	7.2 ± 2.0	6.2 ± 1.9	0.17
OAR motion (mm)	Right kidney	5.2 ± 0.8	5.2 ± 0.6	0.91
	Left kidney	2.8 ± 1.1	3.6 ± 0.5	0.08

be emphasized that this comparison could not be made fair since there were differences in scanners, scanning protocols, evaluators, and evaluation methods. Nevertheless this comparison implies comparable scores in general image quality and vessel definition; comparable tumor-to-pancreas contrast evaluated in the entire volumes; comparable variation in contouring GTVs (note that fixed-delay reported intraobserver variation and optimized-delay reported interobserver variation); better qualitative enhancement score for fixed-delay approach; whereas higher quantitative pancreas enhancement for optimized-delay approach. The last two seemingly contradictory results might be due to the differences in physicians scoring and contouring. Note that some quantities can't be compared because they were not evaluated in both studies.

4. DISCUSSION

Precise and accurate target delineation is critical in modern RT for pancreatic tumors,⁹ particularly with the emerging use of stereotactic body RT.²² This task is difficult because of low tumor-to-pancreas contrast⁷ and large tumor motion.^{5,6} Current RT simulation uses both a CE 3D-CT scan and a 4D-CT scan to address these issues. However, that approach has some limitations. Geometric discrepancies between CE 3D-CT and 4D-CT scans have been reported as resulting from variations in patient position²³ and/or breathing pattern.^{23,24} On average, 12% (up to 50%) of GTVs in 3D-CT fell outside

the ITV in 4D-CT.^{23,24} Delineating the tumor on contrast-enhanced CT is difficult and is even more challenging on unenhanced 4D-CT.⁷ Therefore, surrogates of motion (stent and fiducial markers) are often used in 4D-CT but may not correlate well with tumor motion.⁵⁻⁷

Conceptually, a single CE 4D-CT scan provides an excellent opportunity to accurately delineate the tumor in all phases and simultaneously quantify tumor motion (rather than surrogates of motion). Furthermore, it avoids the geometric discrepancy between the CE 3D-CT and 4D-CT scans. Previous CE 4D-CT for PDA used a fixed-delay approach so that the central part of the pancreas was scanned at 50 s from the start of contrast injection.⁹ The fixed-delay approach was not optimal because it assumed the same injection duration and disregarded large interpatient variations in contrast arrival time. Depending on the amount of contrast medium and injection rate, injection duration may vary significantly (e.g., from 30 to 60 s for 90 ml contrast injected at 1.5–3.0 ml/s). Contrast arrival time was reported to be 20.0 ± 6.2 s (range, 11–32 s) by Van Hoe *et al.* and was 22.8 ± 5.3 s (range, 14.2–34.6 s) in our study. These data support the rationality of our individually optimized timing approach.

CE 4D-CT was comparable to CE 3D-CT and both were better than 4D-CT in terms of image quality scores, tumor-to-pancreas contrast, CNR, and interobserver variation in contouring the GTV. Absolute enhancement levels of pancreas and tumor were higher in CE 4D-CT than in CE 3D-CT because of the larger amount of contrast used (140 and 90 ml, respectively). Both CE 4D-CT and 4D-CT (images at 50% phase) showed higher noise levels than CE 3D-CT. Because a single phase of a 4D-CT was reconstructed with only a small portion (4%–20%, depending on breathing rate and scan parameters) of all projections, its effective mAs per slice (40–200 mAs) was much smaller than that of CE 3D-CT (400 mAs); thus, noise was much higher than that of CE 3D-CT (image noise $\propto 1/\sqrt{\text{mAs}}$). The increased noise in CE 4D-CT led to a slightly worse image quality score, CNR, and interobserver variation compared to CE 3D-CT.

In the diagnostic radiology literature, tumor-to-pancreas contrast is typically evaluated in ROIs manually placed on the center of the tumor, where the relative hypodensity is higher.^{25,26} It was reported that the highest tumor-to-pancreas contrast was obtained in pancreatic phase with 42 HU in Ref. 25 and 49 HU in Ref. 26. On the tumor periphery, the CT

TABLE IV. Comparison of average CT number of pancreas and tumor, tumor-to-pancreas contrast, image noise, and CNR for CE 3D-CT, 4D-CT, and CE 4D-CT.

	CE 3D-CT	4D-CT	CE 4D-CT	Signed rank test (<i>P</i>)		
				CE 3D-CT vs 4D-CT	4D-CT vs CE 4D-CT	CE 3D-CT vs CE 4D-CT
Pancreas (HU)	49.2 ± 12.3	44.6 ± 15.9	75.5 ± 21.2	0.42	<0.001 ^a	<0.001 ^a
Tumor (HU)	53.0 ± 9.2	58.9 ± 14.3	76.3 ± 15.0	0.049 ^a	<0.001 ^a	<0.001 ^a
Tumor-to-pancreas contrast (HU)	15.5 ± 20.7	9.2 ± 9.2	16.7 ± 12.3	0.17	0.001 ^a	0.21
Tumor-to-pancreas contrast (HU) evaluated in entire volumes	15.8 ± 12.8	15.1 ± 10.7	17.6 ± 16.0	0.78	0.40	0.36
Noise (HU)	12.5 ± 3.9	19.4 ± 5.8	22.1 ± 5.7	0.009 ^a	0.39	0.013 ^a
CNR	1.4 ± 1.9	0.6 ± 0.7	0.8 ± 0.6	0.008 ^a	0.014 ^a	0.42

^aSignificant at 0.05.

TABLE V. Interobserver variation in contouring the GTV. Sensitivity, specificity, and Jaccard index measured agreement between individual contour and group consensus contour.

		RA1	RO1	RO2	Average
CE 3D-CT	Sensitivity (%)	67.9 ± 17.5	82.2 ± 17.6	83.8 ± 13.7	78.0 ± 17.4
	Specificity (%)	92.1 ± 10.5	41.2 ± 32.1	87.9 ± 11.9	73.7 ± 30.8
	Jaccard (%)	67.5 ± 15.4	52.1 ± 17.8	78.3 ± 10.0	66.0 ± 18.0
4D-CT	Sensitivity (%)	44.0 ± 22.3	75.2 ± 28.6	80.3 ± 22.6	66.5 ± 28.9
	Specificity (%)	90.6 ± 11.8	48.0 ± 26.6	79.6 ± 24.1	72.7 ± 27.9
	Jaccard (%)	45.6 ± 25.2	46.5 ± 24.1	74.8 ± 23.9	55.6 ± 27.3
CE 4D-CT	Sensitivity (%)	68.0 ± 15.1	72.1 ± 23.6	76.6 ± 17.0	72.2 ± 18.6
	Specificity (%)	89.7 ± 12.9	36.8 ± 21.0	90.9 ± 8.9	72.5 ± 29.5
	Jaccard (%)	69.1 ± 17.2	42.2 ± 18.1	74.4 ± 13.5	61.9 ± 21.3

number difference between the tumor and pancreatic tissues tends to diminish.^{25,26} In fixed-delay CE 4D-CT, tumor-to-pancreas contrast was 60 HU when evaluated in manually placed ROIs (Ref. 9) and was only 2 HU (tumor 44 HU and pancreatic tissues 42 HU) when evaluated in the entire tumor and pancreas volumes.¹¹ This was similar to our result of 17.6 ± 16.0 HU in CE 4D-CT, (Tables IV and V). In this study, the tumor-to-pancreas contrast was evaluated in the regions adjacent to the tumor–pancreas boundary, where it was more relevant for target delineation in RT. Tumor-to-pancreas contrasts in CE 3D-CT (15.5 HU) and CE 4D-CT (16.7 HU) were higher than that in 4D-CT (9.2 HU) (Table IV). When evaluated in the entire tumor and pancreas volumes, the tumor-to-pancreas contrasts were comparable in all three images (15.8, 15.1, and 17.6 HU). Tumor-to-pancreas contrast evaluated in the boundary regions fell between those evaluated in the entire tumor and those evaluated in manually placed ROIs. A few other factors contributed to the small increase of tumor-to-pancreas contrast in CE 3D-CT and CE 4D-CT over 4D-CT. First, the 4D-CT was acquired immediately following the CE 3D-CT, with residual contrast within this time frame so that some contrast enhancement appeared even in the “unenhanced” 4D-CT. Second, three patients had dilated pancreatic ducts that were filled with low-density fluid. This led to lower mean contrast enhancement of normal pancreatic tissues. Third, contrast was injected through the patient’s hand

(rather than arm) at a lower injection rate (<2 ml/s) for three patients. A lower injection rate is known to produce lower contrast enhancement.¹⁴

Tumor volumes defined on 4D-CT tended to overestimate tumor volumes defined on CE 3D-CT and CE 4D-CT. All three physicians reported that the tumor–pancreas boundary was barely detectable and that contouring uncertainty was much higher on the unenhanced 4D-CT. It is suggested that unenhanced CT should not be used for contouring pancreatic tumors. The measured GTV centroid motions were comparable in 4D-CT and CE 4D-CT and agreed well with those reported in the literature.^{6,7}

The large interobserver variations in contouring the GTV (Table V) agreed with a study investigating the same subject among 25 physicians, which reported a median Jaccard index of 57% with an interquartile range of 51%–65%.³ Cattaneo *et al.* reported a mean Jaccard index of $75.1\% \pm 10.3\%$ for intraobserver variation in contouring the GTV on fixed-delay CE 4D-CT.¹¹ Sensitivity, specificity, and Jaccard index were calculated based on STAPLE to quantify interobserver variation. The group consensus contour estimated by STAPLE represents the best agreement of a group of contours and is more robust to outliers than average contour.²¹

5. CONCLUSION

An individually optimized CE 4D-CT technique was developed that demonstrates characteristics comparable to those of CE 3D-CT for PDA simulation. The CE 4D-CT can be acquired safely and has high potential for simultaneously delineating the tumor and quantifying tumor motion with a single scan.

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CONFLICT OF INTEREST DISCLOSURE

The authors have no COI to report.

TABLE VI. Comparison between fixed-delay CE 4D-CT and optimized-delay CE 4D-CT.

CE-4D-CT	Fixed-delay (Refs. 9 and 11)	Optimized-delay	P
Contrast (ml)	140	140	N/A
General image quality	4.0 ± 0.7	3.6 ± 0.8	0.23
Enhancement	4.4 ± 0.5	3.7 ± 0.8	0.02 ^a
Regional vessel definition	4.0 ± 1.3	3.5 ± 0.8	0.30
Pancreas enhancement (HU)	59.7 ± 13.8	75.5 ± 21.2	0.05 ^a
Tumor-to-pancreas contrast (HU) evaluated in entire volumes	2.0	17.6 ± 16.0	N/A
Jaccard index (%)	75.1 ± 10.3	61.9 ± 21.3	0.09
	intraobserver	interobserver	

^aSignificant at 0.05.

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