Evaluation of the potential utility of flat panel CT for quantifying relative contrast enhancement

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Purpose: Certain directed oncologic therapies seek to take advantage of the fact that tumors are typically more susceptible to directed therapeutic agents than normal tissue owing to their extensive networks of poorly formed, leaky vasculature. If differences between the vascularity of normal and tumor tissues could be quantified, patients could be selected for or excluded from directed treatments on the basis of this difference. However, angiographic imaging techniques such as digital subtraction angiography (DSA) yield two-dimensional data that may be inadequate for this task. As a first step, the authors evaluated the feasibility of using a commercial implementation of flat panel computed tomography (FPCT) to quantify differences in enhancement of a simulated tumor compared with normal tissue based on differences in CT number measured in precontrast and postcontrast scans.

Methods: To evaluate the FPCT scanner studied, the authors scanned several phantoms containing simulated normal and tumor tissues. In the first experiment, the authors used an anthropomorphic phantom containing inclusions representing normal, tumor, and bone tissue to evaluate the constancy of CT numbers in scans repeated at clinically relevant intervals of 1 and 3 min. The authors then scanned gelatin phantoms containing dilutions of iodinated contrast to evaluate the accuracy of relative contrast enhancement measurements for a clinical FPCT system. Data were analyzed using widely available software.

Results: CT numbers measured in identical locations were constant over both scan intervals evaluated. Measured relative contrast enhancement values were accurate compared with known relative contrast enhancement values. Care must be taken to avoid artifacts in reconstructed images when placing regions of interest.

Conclusions: Despite its limitations, FPCT in the interventional laboratory can be used to quantify relative contrast enhancement in phantoms. This is accomplished by measuring CT number in simulated tumor and normal tissue on precontrast and postcontrast scans. This information opens the door for refinement of technique in an effort to use such a technique to plan directed therapies.

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I. INTRODUCTION

Many directed oncologic therapies seek to take advantage of the fact that tumors are typically more susceptible to directed therapeutic agents than normal tissue owing to their extensive networks of poorly formed, leaky vasculature. When this is the case, directed therapies that are injected intra-arterially near the tumor are expected to accumulate more in the tumor than in the surrounding normal tissue. Hence, hypervascular tumors would be expected to show a greater response to this type of therapy than patients whose tumors are similarly vascularized compared with the surrounding normal tissue, and this has been demonstrated by several studies that evaluated directed therapy.^{1–3} If the vascularity of tumor compared to surrounding normal tissue could be quantified, patients could be selected for or excluded from directed therapy on the basis of this difference. Recent work has explored the use of digital subtraction angiography (DSA) to quantify

these differences;⁴ however, using two-dimensional images has inherent drawbacks—in particular, an inability to discriminate between overlapping anatomic structures and multiple lesions.

Ideally, the contrast uptake in a tumor compared with that of the surrounding normal tissue would be quantified during a treatment planning session that is as similar to an actual treatment session as possible, as vascular dynamics play a major role in the distribution of many therapeutic agents, including embolic material, after intra-arterial administration. This quantification may be possible by means of flat panel computed tomography (FPCT), which is an option offered on many modern angiographic systems. With this type of system, a catheter can be navigated into an artery and the vascular anatomy mapped using DSA. FPCT scans can be acquired both before and after the injection of a contrast agent, and the enhancement of the tumor and the surrounding normal tissue can be quantitatively compared.

TABLE I. Measured CT numbers using FPCT compared to actual CT number for common materials.

Material	Actual CT number	Measured CT number ^a
Air	−999	−861
Low density polyethylene (LDPE)	−227	−65
Polymethylmethacrylate (PMMA)	29	145
Teflon (PTFE)	1141	922

^aThese data were measured using the FPCT system evaluated in this study.

Before this approach can be considered, the suitability of FPCT for performing such quantification must be evaluated. FPCT is currently used for treatment planning, but only in a qualitative manner, most commonly for searching for additional tumor feeding vessels or clarifying sites of extrahepatic perfusion not clear on DSA.^{5–7} FPCT has also been evaluated for use in brain perfusion imaging, but only by comparing results with perfusion images acquired using conventional CT.^{8,9} It has been shown that FPCT suffers from more artifacts than conventional CT.¹⁰ Artifacts caused by x-ray scattering, changing kilovoltage (kVp) values during the scan, lower beam quality, limited scan angle, and other factors may cause CT numbers to vary widely with differences in patient size and equipment.^{11–15} Also, lag owing to charge trapping in the photodiode layer and afterglow in the scintillator can build up within the image receptor when many frames are acquired in rapid sequence.^{16,17} As a result, CT numbers may be unreliable for absolute quantification (Table I). These limitations indicate that careful evaluation of a FPCT system is needed to assess its utility for quantification.

One way the limitations of FPCT might be overcome is to use it not for absolute quantification but for comparing normal parenchyma and tumor tissue. The goal of this study was to evaluate the possibility of using a commercial implementation of FPCT to quantify differences in enhancement of a tumor compared with normal tissue based on differences in CT number measured in precontrast and postcontrast scans. We evaluated the constancy of measured CT numbers over the course of repeated scans and determined to what degree we could predict the ratio of relative contrast enhancement (RCE) for simulated tumor and normal tissues for a series of multiphase scans.

II. METHODS AND MATERIALS

Three phantoms (described below) were used in the evaluation of the commercial FPCT system used in this study. All of the FPCT scans were performed on a Siemens angiography system (AXIOM Artis dTA) with a 30 cm × 40 cm indirect flat-panel image receptor and an antiscatter grid using DynaCT (Siemens Medical Solutions, Malvern, PA). The parameters for each scan were the same: a 220°, 8-s rotation; a sampling rate of 0.5°/frame; an input dose to the detector of 0.36 μ Gy/frame, with a target kVp of 90. All axial reconstructions were performed using the following parameters: HU/normal algorithm; ring, scatter, truncation, and overexpo-

sure corrections set to “on”; a 1024 × 1024 image matrix with an in-plane resolution of 0.247 mm; and an image thickness of 5 mm. A full set of calibrations for both the flat-panel receptor and the FPCT system were last performed 5 months before this study.

II.A. Constancy of measured CT numbers

Flat-panel image receptors are known to suffer from image degradation caused by residual signal retained within the thin film transistor/photodiode array.^{16,17} While this degradation is transient and typically manifested as artifacts in reconstructed FPCT images, we were concerned that CT numbers measured in reconstructions from multiple scans acquired within a short period of time may show some variation owing to these effects. We used an anthropomorphic phantom (Triple Modality 3D Abdominal Phantom Model 057, CIRS Inc., Norfolk, VA) representing the abdomen to evaluate the constancy of measured CT numbers over the course of repeated FPCT scans. The phantom was scanned a total of five times using two different intervals, with successive scans' start times spaced either 1 or 3 min apart. The 1 min and 3 min interval scans were performed on different days to prevent carryover of any effects from one interval to the other. In addition, a rapid FPCT imaging mode, normally used to acquire images for subtraction, was used to acquire two scans in succession, separated by approximately 2 s. Two sets of native, nonsubtracted images were generated from the two scans and used to reconstruct FPCT images. Square 78.7 mm² ROIs containing approximately 1300 pixels each were defined at locations corresponding to several simulated organs within the phantom; the simulated organs were composed of a wide range of materials and represented normal liver, a liver lesion, and bone (Fig. 1). The same representative slice was evaluated in each image set, and the ROIs were placed at exactly the same locations in each slice.

II.B. Ability to accurately measure relative contrast enhancement

Before this technique can be considered for use with patient images, it is first necessary to demonstrate that known values of RCE can be accurately predicted in a controlled situation. We constructed two gelatin phantoms to determine whether RCE could be measured accurately. The phantoms were cast in molds with holes drilled to accept 20 cc

FIG. 1. Locations of regions of interest in an anthropomorphic phantom used to evaluate CT number constancy, representing (a) normal liver, (b) tumor, and (c) bone.

TABLE II. Iodinated contrast medium dilutions used in this study.

Ratio of iodinated contrast medium to water	CT number
Water only	0
1:250	30
1:200	38
1:150	49
1:100	75
1:50	154
1:25	308

syringes filled with serial dilutions of iodinated contrast medium (Optiray 320; Mallinckrodt Inc., Hazelwood, MO) in water in ratios representing the range of CT numbers expected during precontrast and postcontrast scans of patients' livers (Table II) using our FPCT system, with pure water used to represent normal tissue precontrast. Phantom 1 was rectangular in shape and exceeded the scan field of view (SFOV) of the FPCT scanner, which resulted in truncation artifacts in the reconstructed FPCT images. Phantom 2 was cylindrical in shape and 20 cm in diameter, and was fully contained within the SFOV. Sets of five (Phantom 1) or four (Phantom 2) water-filled syringes were placed in the holes in the phantoms to simulate a precontrast scan. Postcontrast scans were simulated by replacing all but one water-filled syringe (numbers 1, 2, 3, and 5 in Fig. 2 and numbers 1, 2, and 3 in Fig. 3) with syringes containing either a 1:150 or 1:200 dilution of iodinated contrast agent and the last water-filled syringe (number 4 in Figs. 2 and 3) with a single syringe containing a higher concentration of the agent (1:25, 1:50, or 1:100). The 1:150 or 1:200 dilution represented normal parenchymal enhancement, while each of the higher concentrations represented a tumor with a different level of enhancement.

RCE was calculated as

$$\text{RCE} = \frac{\text{CT}_{\text{tumor post}} - \text{CT}_{\text{tumor pre}}}{\text{CT}_{\text{parenchyma post}} - \text{CT}_{\text{parenchyma pre}}}, \quad (1)$$

where CT_x was the CT number measured in the simulated tumor or normal liver parenchyma in precontrast or postcontrast FPCT scans. The 1:100 and 1:25 dilutions predicted RCE values of 1.5:1 and 6:1, respectively, when the 1:150 dilution was used to represent normal parenchymal enhancement, and the 1:50 dilution predicted a RCE value of 4:1 when used with the 1:200 dilution. One set of scans was performed using five

FIG. 2. Location and identification of regions of interest in Phantom 1 used to measure RCE.

FIG. 3. Location and identification of regions of interest in Phantom 2 used to measure RCE.

1:150 dilution-containing syringes, resulting in a predicted RCE value of 1:1. For each dilution level and phantom, a “precontrast” scan was obtained, syringes were swapped, and a “postcontrast” scan was acquired. Square 98.3 mm² ROIs containing approximately 1600 pixels each were placed in the same representative slice in each reconstruction (Figs. 2 and 3). CT numbers were measured and RCE values determined using each of the three or four identical dilutions representing normal parenchyma. All images were exported from our PACS system and evaluated using ImageJ v. 1.44e (National Institutes of Health, Bethesda, MD).

III. RESULTS

III.A. Constancy of measured CT numbers

Table III lists the measured CT numbers and their associated coefficients of variation in series of five images acquired either 1 min apart or 3 min apart and for the rapid FPCT imaging mode. The CT number was essentially constant in each

TABLE III. Constancy of CT numbers across multiple FPCT scans.

Tissue simulated	Interval		
	1 min	3 min	Rapid mode ^a
Liver			
CT number range ^b	109.2–111.9	104.3–106.8	55.8–56.0
Mean CT number (SD)	110.2 (1.1)	105.9 (0.98)	55.9 (0.19)
Coefficient of variation (%)	0.99	0.92	0.34
Liver lesion			
CT number range	55.2–56.6	61.0–61.8	–15.7 to –16.4
Mean CT number (SD)	55.9 (0.55)	61.4 (0.31)	–16.1 (0.54)
Coefficient of variation (%)	0.98	0.51	3.4
Bone			
CT number range	487.3–488.8	467.5–470.1	320.6–321.5
Mean CT number (SD)	487.9 (0.54)	468.9 (1.1)	321.0 (0.65)
Coefficient of variation (%)	0.11	0.23	0.20

^aRapid mode acquired two FPCT scans in rapid succession, separated by the time required to return C-arm to start position, approximately 2 s. Data represent CT number measured in only the two scans acquired in this mode, not a series of 5 as in the 1 and 3 min intervals. This mode also used different scan techniques compared to the 1 and 3 min intervals.

^bCT number range is the range of CT numbers across the five images acquired at each time interval. Mean and standard deviation were calculated using the five measurements made in each region from all the scans.

TABLE IV. RCE values measured in Phantom 1.

Predicted RCE value	Measured RCE value (percent error)				
	Position 1	Position 2	Position 3	Position 4	Position 5
6:1	6.1:1 (1.2)	6.5:1 (7.2)	6.0:1 (0.1)	–	5.8:1 (–4.0)
4:1	4.0:1 (–0.1)	4.0:1 (1.1)	4.3:1 (7.5)	–	3.9:1 (–2.4)
1.5:1	1.3:1 (–12.3)	1.6:1 (6.5)	1.5:1 (–0.1)	–	1.5:1 (0.6)
1:1	0.90:1 (–10.6)	0.95:1 (–4.7)	0.98:1 (–2.4)	–	1.3:1 (22.3)

region across multiple scans acquired at these clinically relevant intervals, with a maximum coefficient of variation (COV) of 0.99% for the five scan series and a maximum COV of 3.4% for the rapid imaging mode, for which only two scans were analyzed. The absolute CT numbers measured were different in the rapid FPCT imaging mode because it used a higher kVp than the conventional FPCT imaging mode.

III.B. Ability to accurately measure known relative contrast enhancement

Table IV lists the RCE values measured in Phantom 1 for contrast medium dilutions with predicted RCEs of 6:1, 4:1, 1.5:1, and 1:1. The measured RCE in Phantom 1 varied between –12% and +7.5% compared to the predicted RCE values, with the exception of the use of the ROI at position 5 as the “normal” tissue, which varied by as much as +22%. This error was caused by a ring artifact that was present in the central region of each image (Fig. 4). This artifact affected the measured CT number for the ROI at position 5, resulting in measured RCE values with larger errors than those measured using other ROIs.

Table V lists the RCE values measured in Phantom 2 for contrast medium dilutions with predicted RCEs of 6:1, 4:1, 1.5:1, and 1:1. The measured RCE in Phantom 2 varied between –9.0% and +3.6% compared to the predicted RCE values. In addition, measured RCE values for the smaller phantom (Phantom 2) matched actual RCE values more closely than did RCE values measured in the large phantom (Phantom 1).

While the percent error was large in some cases, especially for the 1:1 simulated RCE, the absolute magnitude of errors in RCE measurements was generally similar for all simulated

RCE values. Precontrast and postcontrast scans for both phantoms were acquired at intervals ranging from 3 to 5 min, as the earlier experiment had demonstrated that the measured CT numbers did not depend on scan interval.

IV. DISCUSSION

Our data demonstrate that CT numbers measured at the same locations in FPCT images were constant across multiple scans at clinically relevant scan intervals. Also, RCE values measured on FPCT images were accurate. Measured RCE values were more accurate in Phantom 2, which was fully contained within the SFOV, than in Phantom 1, which exceeded the SFOV. This result is likely attributable to increased scatter and beam hardening (as well as corrections applied to account for these effects) in the larger phantom. The large phantom more closely represents the clinical scenarios most often encountered in administration of directed therapy.

These data also demonstrate that care must be taken in positioning ROIs when measuring RCE. When artifacts are present, large errors in measured RCE values may result. In this analysis, artifacts were most severe in the center of reconstructed images, corresponding to the center of the SFOV. Therefore, if this imaging system were to be used for quantifying RCE, a tumor for which RCE is being determined should be positioned away from the center of the SFOV and measurements in normal tissue should not be made at the center of the SFOV or near other artifacts. Regular calibration of the FPCT imaging mode should also be performed to reduce the appearance of artifacts. In addition, care must be taken to place ROIs in the same z-axis location in the precontrast and postcontrast scans and to avoid any gross patient motion between the precontrast and postcontrast scans, as the cone beam imaging geometry leads to some nonuniformity in CT number along the z-axis (Fig. 5). It can be concluded, based on these results, that FPCT can be used for quantification of *relative* contrast enhancement in phantoms. The magnitude of the errors of measured RCE values, presented in this manuscript, can be used to determine RCE ranges that can be used to classify patients' tumors and identify patients who may benefit from directed therapy.

The results presented here can be used to begin to describe a method for using a FPCT system to measure RCE values for tumors in patients. The position of the patient should be the same for both the precontrast and postcontrast scans, and ROIs should be placed in the same z-axis location in such a way as to avoid any artifacts present in the FPCT images.

FIG. 4. Images of the (a) anthropomorphic phantom and (b) gelatin phantom demonstrating ring artifacts that interfered with RCE quantification.

TABLE V. RCE values measured in Phantom 2.

Predicted RCE value	Measured RCE value (percent error)			
	Position 1	Position 2	Position 3	Position 4
6:1	6.2:1 (3.6)	5.8:1 (−3.8)	5.9:1 (−0.9)	—
4:1	4.1:1 (2.4)	4.0:1 (0.7)	4.1:1 (2.7)	—
1.5:1	1.4:1 (−7.3)	1.4:1 (−9.0)	1.4:1 (−4.2)	—
1:1	0.96:1 (−4.3)	1.0:1 (−0.5)	0.99:1 (−1.3)	—

The postcontrast scan should be acquired as soon as possible after the precontrast scan to minimize the likelihood of gross patient motion. While our RCE experiment could not be repeated in the rapid FPCT imaging mode because it was not physically possible to swap syringes in the phantom in the time required (~ 2 s) for the C-arm to reposition itself for the second scan, patient imaging would be possible using the rapid imaging mode because the contrast injection could be timed to start automatically. In some cases, the presence of metallic objects within the field of view, such as embolization coils, may preclude the use of this method. As it is uncertain whether or not the results presented here can be generalized to other FPCT systems, the tests described here should be used to characterize each FPCT system that will be used for treatment planning to assess its suitability for the task. Extension of this method to patient images will also require investigation of contrast enhancement dynamics, including the injection timing and contrast volume required to reach a steady state of contrast enhancement within a tumor.

Our work had several limitations. In a patient, all normal parenchyma would be enhanced after a contrast injection, not just isolated areas as simulated in this study. However, this limitation does not negate our conclusions because although the additional filtration of the x-ray beam through this contrast-enhanced parenchyma would change the measured CT numbers, the RCE values, by definition, should not be affected. Another limitation of the current study is that we evaluated the accuracy of RCE values using only simple phantoms. Imaging of anatomically complex regions or of very

large or small patients may cause unique artifacts in FPCT images that could affect the accuracy of the calculated RCE values or prohibit the use of this method. A previous attempt by other investigators to quantify the tumor to normal ratio using DSA was hampered by breathing motion and the influence of superimposed anatomy.⁴ The method described in this work is not influenced by superimposed anatomy, however, the impact of breathing motion has not been determined.

V. CONCLUSIONS

This study has shown that a commercial implementation of FPCT on a modern angiographic system can be used for specific quantitative measurements. In addition, we have verified the accuracy of a simple method for quantifying the RCE of simulated tumors compared with normal tissue by placing carefully selected ROIs on precontrast and postcontrast FPCT images. This method may ultimately be useful for guiding medical decision-making about the use of directed therapy. However, further investigation is required to develop and refine this technique before turning it into a tool for patient care.

Future work should be directed toward determining the simplest and most reliable way to measure RCE values in patient images. This includes determining the optimal method for placing ROIs in patient images, as large vessels can cause artifacts in images and contrast uptake within tumors is often nonuniform. Also, the kinetics of enhancement during intra-arterial contrast administration must be studied to determine the optimal injection protocol for reliable and repeatable measurement of RCE.

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FIG. 5. Plot of relative CT number, normalized to $z = 0$, along the z -axis of the FPCT scanner.

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