Ablation zone visualization enhancement by periodic contrast-enhancement computed tomography during microwave ablation

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Purpose: Intra-procedural contrast-enhanced computed tomography (CECT) has been proposed to monitor the growth of thermal ablations. The primary challenge with multiple CT acquisitions is reducing radiation dose while maintaining sufficient image quality. The purpose of this study was to evaluate the feasibility of applying local highly constrained backprojection reconstruction (HYPR-LR) on periodic CECT images acquired with low-dose protocols, and to determine whether the ablations visible on CT were commensurate to gross pathology.

Methods: Low-dose ($CTDI_{vol} \leq 1.49 \text{ mGy}$), temporal CECT volumes were acquired during microwave ablation on normal porcine liver. HYPR processing was performed on each volume after image registration. Ablation signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) were collected to evaluate the degree of enhancement of image quality and ablation zone visualization. Ablation zones were manually segmented on HYPR and non-HYPR images and compared spatially using Dice's coefficient. The dimensions of ablation zones were also compared to gross pathology by correlation and dimensional differences.

Results: The SNR and CNR of ablation zones were increased after HYPR processing. The manually segmented ablation zone was highly similar to gross pathology with a Dice coefficient of 0.81 ± 0.03 , while the low-dose CECT had a smaller Dice coefficient of 0.72 ± 0.05 . Both HYPR and low-dose CECT had high correlation to gross pathology (0.99 and 0.94, respectively), but the variance of measurements were lower after HYPR processing compared to unprocessed images. The relative difference in area, length of long axis, and length of short axis for HYPR image were $13.1 \pm 5.6\%$, $9.7 \pm 4.2\%$, and $15.2 \pm 2.8\%$, which were lower than those for low-dose CECT at $37.5 \pm 6.0\%$, $17.7 \pm 2.8\%$, and $28.9 \pm 5.4\%$.

Conclusion: HYPR processing applied to periodic CECT images can enhance ablation zone visualization. HYPR processing may potentially enable CECT in real-time ablation monitoring under strict regulation of radiation dose. © 2017 American Association of Physicists in Medicine [<https://doi.org/10.1002/mp.12266>]

Key words: ablation monitoring, computed tomography, microwave ablation, thermal ablation, visualization enhancement

1. INTRODUCTION

Thermal ablation has been widely adopted as a treatment for focal tumors in the abdomen and chest due to the minimally invasive approach, shorter time for recovery, fewer and less serious complications, and suitable efficacy compared to traditional surgical resection.^{1–10} Generally speaking, percutaneous ablation therapy is performed by placing a thin applicator into a target region under imaging guidance. Energy such as radiofrequency (RF) electrical current or microwaves is delivered through the applicator to heat and destroy the targeted tissue.^{1,3,11–15}

Ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) is used to guide, monitor and follow

percutaneous ablation treatments. However, several studies have identified challenges in differentiating the ablation zone, untreated malignant tissue, and normal tissue.^{16,17} Several research groups have evaluated intra-procedural ablation monitoring by sequential ultrasound,^{18,19} but these techniques have been hampered by signal backscatter due to bubbles produced during water vaporization, and are commonly limited to a single imaging plane.²⁰ While MRI with or without contrast can also provide information about ablation zone growth and post-procedure ablation assessment, its high cost and a lack of MRI-compatible ablation devices limit its use broadly.^{21,22} Consequently, contrast-enhanced CT (CECT) is a common technique for immediate volumetric assessment of the ablation zone and relevant adjacent structures.²⁰

Recent studies have also described techniques for intra-procedural ablation monitoring with CT, either with or without iodinated contrast. Goldberg et al. utilized CT fluoroscopy combined with ultrasound imaging to target the applicator and visualized ablation zone.¹⁶ Schena et al. derived the relationship between Hounsfield units (HU) and temperature by experiments and then utilized it in real-time temperature monitoring of laser ablation.²³ When using contrast, some of the iodine may become trapped in the ablation zone, slightly affecting visualization of the ablation zone but does not preclude the use of serial CT for ablation monitoring.²⁴

Maintaining a total radiation dose and iodinated contrast load at or below conventional abdominal CT levels is an important objective to allow for wider adoption of serial CT for ablation monitoring. Since reductions in both radiation and iodine dose will degrade image quality, techniques to recover the lost information and render imaging volumes suitable for assessment of the ablation zone growth are necessary.^{25,26}

Highly constrained backprojection (HYPR) can improve signal fidelity and reduce image noise in angiography applications, and has been applied to serial CT of thermal ablations.^{27–29} While those prior studies showed an improvement in ablation zone visibility, they did not evaluate whether the visible ablation zone matched gross pathologic evidence of tissue necrosis.²⁹ The purpose of this study was to investigate the radiological-pathological correlation of serial contrast-enhanced CT with HYPR post-processing and explanted ablation zones in an in vivo liver model.

2. MATERIALS AND METHODS

2.A. In vivo ablation procedure

A total of six microwave ablations were performed in the livers of four female domestic swine (Agricultural Research Station, Arlington, WI, USA) with a median weight of 65 kg (range, 50–70 kg), with a mean of two ablations per animal. The animal was sedated with 7 mg/kg of intramuscular tiletamine hydrochloride and zolazepam hydrochloride (Telazol; Wyeth, Fort Dodge, IA, USA) and 2.2 mg/kg of xylazine hydrochloride (Xyla-Ject; Phoenix Pharmaceutical, St Joseph, MO, USA). Endotracheal intubation was facilitated by means of 0.05 mg/kg atropine (Phoenix Pharmaceuticals, Burlingame, CA, USA), and then anesthesia was induced and maintained the effect with 2% inhaled isoflurane (Halocarbon Laboratories, River Edge, NJ, USA). Once anesthetized, the animal was placed supine on the CT scanner bed (General Electric 750 HD, Waukesha, WI, USA). The liver was surgically exposed before ablation, and up to three triaxial antennas (LK 15; NeuWave Medical Inc., Madison, WI, USA) were visually placed into separate lobes. A 2–3 mm barbed metal hook was placed into the surface of the liver near each antenna to serve as a fiducial marker for co-registration between radiological imaging and gross pathology data. An initial 40 ml of iodinated contrast agent (300 mg/ml iohexol, GE Healthcare, Waukesha, WI,

USA) was injected approximately 1 min before microwave power delivery at 5 ml/s. To maintain contrast enhancement during serial CT, 10 ml of contrast agent was delivered 1 min before each scan at 3 ml/s. The ablation was then created by a 2.45 GHz MW generator (Certus 140; NeuWave Medical Inc., Madison, WI, USA) with 100 W delivered through the antenna for 10 min. The swine were euthanized after ablation and their livers were removed. Each ablation was sliced along the antenna axis in a plane coincident with the barbed hook fiducial and then photographed to provide a “ground truth” pathological assessment.

2.B. Image processing

Serial abdominal CECT (80 kVp, 100 mAs, 512×512 , 1:0.984 helical pitch, 1.25 mm slice thickness) was performed at 1 min intervals (total 10 scans) during the ablation. Accumulated radiation dose ($CTDI_{vol}$) was computed for each scan. The initial CT volume was rotated according to the insertion angle of the applicator to ensure slices were perpendicular to applicator. Subsequent volumes were then co-registered to the first volume by aligning applicators under rigid assumptions.³⁰ Metal artifacts in each volume were reduced slice by slice by forward projecting each image, replacing the metal attenuation data in the sinogram using sparse interpolation, and then back projecting the result.^{25,31,32} HYPR processing was then applied slice by slice according to procedures outlined previously.²⁸ A brief summary of the steps is provided here. First, a composite image is formed:

$$I_H(x, y, z; t_N) = I_c(x, y, z; t_N) \cdot \frac{I(x, y, z; t_N) * F(x, y)}{I_c(x, y, z; t_N) * F(x, y)}, \quad (1)$$

where $I(x, y, z; t_N)$ is the slice at the latest time t_N and $I_c(x, y, z; t_N)$ is the composited slice, which is the temporal average of previous and current slices,

$$I_c(x, y, z; t_N) = \frac{1}{N} \sum_{i=1}^N I(x, y, z; t_i), \quad (2)$$

$F(x, y)$ is a 2D 10×10 pixel uniform square low pass filter (LPF) which was applied on every slice. The symbol “*” means 2D convolution. N is total time frames for serial CECT, which was 10 in this study. The final output slice $I_H(x, y, z; t_N)$ was calculated through multiplying the composited slice by the weighting slice to effectively enhance changes introduced in the latest slice (Fig. 1). All CECT volumes were processed using MATLAB 2015a on Intel Core i7 2.80 GHz processor and 8 GB memory.

2.C. Statistical analysis

Six concentric regions of interests (ROIs) with approximately 3 mm thickness were selected around the applicator from six slices in the central ablation at each time point (Fig. 2). The signal-to-noise ratio (SNR) and contrast to noise ratio (CNR) of each ROI, which quantified the image quality and visibility of ablation zone, respectively,

FIG. 1. Flow diagram of HYPR algorithm (MDT = metal artifact reduction, LPF = low pass filter).

FIG. 2. Flowchart of pre-processing and design of predefined ROI of ablation zone, which fully covered of the real ablation zone (black and grey region around the applicator). [Color figure can be viewed at wileyonlinelibrary.com]

$$SNR = \frac{\mu_{abl}}{\sigma_{background}}, \quad (3)$$

$$CNR = \frac{\mu_{liver} - \mu_{abl}}{\sigma_{background}}, \quad (4)$$

where μ_{abl} is the weighted average attenuation with respect to each ROI inside ablation zone by the following formula,

$$\mu_{abl} = \frac{\sum_{i=1}^6 A_i \mu_i}{\sum_{i=1}^6 A_i}, \quad (5)$$

A_i is the area of i -th ring ROI, μ_i is the average attenuation of i -th ring ROI, μ_{liver} is the mean attenuation of the background liver extracted from predefined ROI, (a 15×15 pixel square manually located on the liver region without overlapping the ablation zone, air or gallbladder), on each slice at each time point. $\sigma_{background}$ is the image noise calculated as the standard deviation of attenuation in the background air. Mean and standard error of SNR and CNR were calculated across six separate samples to represent the general temporal variation during the ablation procedure. At each time frame, SNR and CNR in unprocessed and HYPR-processed data were compared by two-sample t -tests.

2.D. Ablation zone analysis

Unprocessed and HYPR-processed CT ablation data were created by virtually slicing the volume along the antenna.³³ In brief, the initial virtual slicing plane was generated by the vector which acquired from rotating the normal vector of xz-plane according to the applicator angle. This initial plane was

then rotated about the applicator to identify the plane containing the hook fiducial (Fig. 3).

Gross pathology was co-registered and rescaled to the radiological virtual slice from the last time point according to the location and length of the antenna and hook fiducial. Three independent observers (3–5 yr research experience in thermal ablation each) manually segmented the ablation zone on the raw and HYPR-processed virtual slices and gross pathology by delineating along the sharp transition of color or attenuation using ImageJ (National Institutes of Health). All six ablation zones on both radiological and pathological images were measured by each observer. Dice's coefficient was used to quantitate similarity between CT images and gross pathology, and to examine similarity between observers³⁴

$$DICE = \frac{2J}{1+J}, \quad (6)$$

where J is a Jaccard index. For radiological–pathological comparison,

$$J_{path-rad} = \frac{A_{path} \cap A_{rad}}{A_{path} \cup A_{rad}}, \quad (7)$$

where A_{path} and A_{rad} were the pathological and radiological ablation segmentation masks, for a given observer. Similarity between radiology and pathology were then evaluated from the mean and standard deviation of the Dice coefficients from all observers. To evaluate intra-observer agreement,

$$J_{intra} = \frac{A_1 \cap A_2 \cap A_3}{A_1 \cup A_2 \cup A_3}, \quad (8)$$

FIG. 3. The schematic of virtual slicing (a) the generation of normal vector of initial virtual slicing plane. (b) the initial virtual slicing plane was then rotated to acquire the largest ablation zone in the volume. ($\vec{n}_{xy}$: the normal vector of xz-plane; $\vec{n}_{vp}$: the normal vector of initial virtual slicing plane).

where A_n was the segmentation mask generated by the n -th observer for radiological images. Agreement between observers was characterized by the mean and standard deviation of this Dice coefficient. A paired-sample t -test was performed using each set of Dice coefficients to compare radiological–pathological agreement and intra-observer variability between unprocessed and HYPR-processed CT data.

Long- and short-ablation dimensions were delineated by straight lines passing through the ablation center. The correlation between measurements made at CT and gross pathology were quantified by Pearson's coefficient. The intra-observer agreement of measurements for gross pathology, original CT and HYPR images was quantified by averaging relative standard deviation (RSD), which is the ratio of standard deviation to the mean, among all samples. The mean and standard deviation of RSD were used to analyze the reliability of measurement. The paired-sample t -test of RSD between radiological images and gross pathology was used to analyze the reproducibility of measurement, which was highly related to the visibility of ablation zone displayed on original CT and HYPR images. The absolute difference (A.D.) and relative difference (R.D.) of measurements between radiological and pathological images were used to quantitate the shape difference of ablation zone by the following formula:

$$A.D. = |M_{rad} - M_{path}| \quad (9)$$

$$R.D. = \frac{A.D.}{M_{path}} \quad (10)$$

Where M_{path} and M_{rad} are the pathological and radiological measurements.

3. RESULTS

3.A. Radiation dose and processing time

$CTDI_{vol}$ was a maximum of 1.49 mGy for each intra-procedural scan. Total radiation dose per procedure was under 14.9 mGy, which is comparable to a typical contrast-enhanced abdominal exam. Average time to process a CECT

volume, including image registration and HYPR processing, was 9.2 s (registration: 7.5 s; HYPR: 1.7 s).

3.B. Statistical analysis

The image quality of HYPR-processed ablation zones increased significantly after two time frames and remained about two times greater than unprocessed data (Fig. 4(a)). Differences in SNR were statistically significant between groups. Ablation zones were about twice as visible, as measured by CNR, in HYPR-processed images compared to unprocessed imaging after about 4 minutes of ablation (Fig. 4(b)).

3.C. Ablation zone similarity analysis

In CT images from the final time frame, attenuation near the ablation border was decreased by thermal expansion of tissue water.^{20,35} However, increased noise in unprocessed low-dose images made the ablation boundary more ambiguous (Fig. 5). Compared to unprocessed images, HYPR-processed images preserved the central vapor region and enhanced visualization of the coagulation region near the border, making the ablation boundary more visible (Fig. 5). Ablation zones segmented from HYPR-processed images were more similar to gross pathology compared those segmented from unprocessed CT images (path-rad similarity: HYPR = 0.81 ± 0.03 , Unprocessed = 0.72 ± 0.05 ; $P = 0.06$; Table I). In addition, there was greater consistency of segmentation among observers from HYPR-processed images compared to unprocessed images (intra-observer similarity: HYPR = 0.79 ± 0.06 , Unprocessed = 0.70 ± 0.16 ; $P = 0.17$; Table I).

3.D. Measurement variability analysis

The mean relative pathological–radiological difference in areas which were segmented by multiple observers from HYPR-processed images was significantly lower than unprocessed images (HYPR = $13.1 \pm 5.6\%$, unprocessed = $37.5 \pm 6.0\%$; $P = 0.003$; Table II). A similar trend was noted

FIG. 4. Mean temporal (a) SNR and (b) CNR and the temporal P -value for (c) SNR (in $\log_{10}$ -scale) and (d) CNR. Plots for mean measurement showed as "Mean $\pm$ Standard error". [Color figure can be viewed at wileyonlinelibrary.com]

in diameter measurements, though with a smaller pathological–radiological difference in the long axis (long axis: HYPR = $9.7 \pm 4.2\%$, unprocessed = $17.7 \pm 2.8\%$; $P = 0.10$; short axis: HYPR = $15.2 \pm 2.8\%$, unprocessed = $28.9 \pm 5.4\%$; $P = 0.05$; Table II). These results suggest that HYPR-processed images provided more reliable detection of the ablation zone dimensions than unprocessed images.

3.E. Dimension and area correlation analysis

Ablation zones segmented from both HYPR-processed and unprocessed images were highly correlated with gross pathology (Table III). HYPR provided a greater correlation between imaging and pathology in terms of ablation area (Fig. 6(a)). The correlation of short axis length on both images relative to pathology was also high (Fig. 6(c)), but the correlation coefficient of the long axis length was higher

on HYPR images than unprocessed images (Fig. 6(b)). This suggests that ablation length was the major difference between unprocessed images and gross pathology.

In looking at agreement between observers, RSDs of all measurements from HYPR images were closer to those of gross pathology compared to unprocessed images (Table IV). In essence, the human error in measurement for HYPR images was similar to that of the ground truth: gross pathology. Greater error was noted when segmenting unprocessed images.

4. DISCUSSION

In this study, we investigated the feasibility of using serial low-dose CECT with HYPR processing to monitor growing microwave ablations. Analysis of image quality metrics SNR and CNR indicated that HYPR processing improves image quality and enhances visualization of the ablation zone

FIG. 5. Example result of manual segmentation on HYPR and unprocessed data. (a) HYPR with high similarity of segmentation between observers, (b) unprocessed data with ambiguous ablation zone segmentation, (c) gross pathology. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE I. Similarity of ablation zone between radiological and pathological image.

	Path. vs. Rad.			Intra-observer		
	Mean DICE coefficient	Minimum DICE coefficient	Maximum DICE coefficient	Mean DICE coefficient	Minimum DICE coefficient	Maximum DICE coefficient
Unprocessed	0.72 ± 0.05	0.53	0.86	0.70 ± 0.16	0.41	0.82
HYPR	0.81 ± 0.03	0.73	0.89	0.79 ± 0.06	0.73	0.88

Data provided as mean $\pm$ standard deviation.

TABLE II. Measurement of difference between radiological and pathological image.

	Absolute difference (cm or cm ²)			Relative difference (%)		
	Mean	Maximum	Minimum	Mean	Maximum	Minimum
Unproc.						
Area	6.09 ± 1.44	17.30	0.15	67.0 ± 24.3	167.8	0.9
LA	1.18 ± 0.31	3.11	0.05	23.5 ± 7.4	84.8	0.7
SA	1.07 ± 0.25	2.18	0.16	44.0 ± 18.7	131.3	5.8
HYPR						
Area	1.84 ± 0.61	4.75	0.02	16.7 ± 11.3	69.6	0.2
LA	0.64 ± 0.22	1.72	< 0.01	11.1 ± 6.6	40.4	$< 10^{-3}$
SA	0.50 ± 0.14	1.02	0	18.1 ± 3.8	39.6	0

Data provided as mean $\pm$ standard deviation. Unproc., unprocessed.

(Fig. 4). Correlation analysis suggested that the dimension and shape of ablation zones extracted from the final CECT-HYPR images were highly correlated with gross pathology, and CECT-HYPR data provided greater ablation clarity compared to unprocessed images (Fig. 6; Table III). The time to process a single volume, including image registration and HYPR processing, was only 9.2 s and less than the minimal time interval between CECT acquisitions (15 s). Therefore, this study demonstrated the feasibility of using low-dose CECT to perform real-time ablation monitoring.

HYPR processing involves two important parts to improve image quality and enhance visualization of the ablation zone: (a) compositing and (b) weighting. The composited slice, which is average of images at previous time frames, can reduce random noise.²⁸ In addition, averaging images at previous time frames can also accumulate the enhancing effects from continuous contrast agent delivery on normal liver.²⁹ Therefore, contrast between the ablation zone and background increases, making the ablation zone more visible with each new set of CT images. The weighting slice, which is the

TABLE III. Pathological–radiological correlation coefficients of before and after HYPR.

	Unprocessed			HYPR		
	Area	LA	SA	Area	LA	SA
Coefficient	0.94	0.73	0.95	0.99	0.90	0.92
R^2	0.89	0.53	0.91	0.99	0.82	0.85
P	0.005	0.101	0.003	$<10^{-4}$	0.013	0.009

LA, long axis; SA, short axis.

ratio between the filtered current and composited slices, augments changes that have occurred in the current time frame.

Multiplying the composited and weighting slices together preserves current geometric information including the shape of ablation zone at current time frame, which could make enhanced image truly display current ablation zone. Hence, the whole HYPR procedure could enhance and truly visualize current ablation zone.

Ablation areas measured from unprocessed CECT images tended to overestimate areas from gross pathology (Fig. 6), which supports prior studies.^{36,37} Hyperthermia induced in the ablation periphery can cause water expansion, and gas produced in the central ablation region will expand into the periphery. Both effects would be expected to lower x-ray attenuation slightly, though potentially not enough to be discernable depending on local image noise. Compared to

FIG. 6. Path-rad correlation of (a) area, (b) long axis, and (c) short axis for HYPR and unprocessed data. Fit and correlation metrics are noted in Table III. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE IV. Measurement of relative standard deviation.

	Path.	Rad.- HYPR	Rad.- Unproc.	P-value (Rad.- HYPR vs. Path.)	P-value (Rad.- Unproc. vs. Path.)
Area	0.17 ± 0.10	0.18 ± 0.08	0.27 ± 0.17	0.78	0.21
LA	0.04 ± 0.03	0.10 ± 0.08	0.12 ± 0.06	0.08	0.04
SA	0.13 ± 0.09	0.10 ± 0.06	0.20 ± 0.18	0.32	0.22

Data provided as mean ± standard deviation. Unproc., unprocessed; LA, long axis; SA, short axis.

unprocessed data, the linear regression of CECT-HYPR has less overestimation of the area measured at gross pathology, demonstrating the ability of HYPR to compensate for increased image noise. The fitted line also demonstrated that the CECT-HYPR area matched well with gross pathology when ablation dimension was less than 25 cm², which includes most ablations produced with less than 100 W.³⁸ Imaging performed during ablation at higher powers and longer treatment times may not provide the same correlation with gross pathology. The 5 mm error in HYPR-processed diameter measurements is within the desired ablation safety margin, which is 5 to 10 mm circumferentially depending on tumor type.³⁹ In addition, HYPR-processed images led to greater agreement (i.e., less variability) between observers than unprocessed images.

Similarity metrics and correlation between pathological and radiological images indicated that the ablation zones visualized from HYPR-processed images were more similar to gross pathology than prior studies (Fig. 6; Tables I, II and III). For example, DeWall et al. analyzed images obtained with shear wave velocity (SWV) during microwave ablation in *ex vivo* bovine liver.⁴⁰ Mean Dice's coefficients between images and gross pathology ranged from 0.74 to 0.77, with Pearson coefficients of 0.54–0.80. These values are all lower than our investigation from CECT-HYPR images (Tables I and III). Considering the single image plane limit in ultrasound imaging, these results suggested that HYPR processing on CECT volume could be more helpful to visualize the complete ablation volume.

Several weaknesses and limitations in data processing and analysis exist. First, rigid assumptions were used for registration based on the assumption that breathing only causes applicator to shift and rotate during ablation. Abdominal structures or the applicator may elastically deform during breathing; however, preliminary analysis of the applicator suggested minimal deformation leading to registration errors of around 1 mm. Even with potential errors, the analysis in our study still suggested that HYPR could improve the visualization of ablation zones. Our results could be the baseline to further study on using different registration methods with the HYPR algorithm. Second, we only performed pathology–radiology correlation analysis and similarity measurements on the data from the last time frame as this was the closest point to when gross pathology was obtained. While we cannot confirm similar correlation for all time points, the temporal

trends of ablation growth we observed were monotonically increasing during each procedure. The same increase is expected regardless of the treatment time and power delivery.^{38,41–43}

In conclusion, we performed HYPR processing on time-series CECT volume during ablation procedure. The results showed that HYPR processing could improve the image quality and enhance visualization of ablation zone, leading to more consistent manual segmentation by observers. The segmented HYPR ablation lesion was more similar to gross pathology, suggesting that HYPR processing may help offset image quality loss from dose reduction strategies. Future studies will focus on analyzing the amount of radiation dose reduction that the HYPR algorithm could tolerate to improve ablation zone visualization. Another direction of future studies will be evaluating whether improved intra-procedural imaging helps to increase the efficacy of ablation treatments.

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