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Abstract. Laser interstitial thermal therapy (LITT) has recently emerged as a new treatment modality for cancer pain management that targets the cingulum (pain center in the brain) and has shown promise over radio frequency (RF)-based ablation, due to magnetic resonance image (MRI) guidance that allows for precise ablation. Since laser ablation for pain management is currently exploratory and is only performed at a few centers worldwide, its short- and long-term effects on the cingulum are currently unknown. Traditionally, treatment effects for neurological conditions are evaluated by monitoring changes in intensities and/or volume of the ablation zone on post-treatment Gadolinium-contrast T1-w (Gd-T1) MRI. However, LITT introduces subtle localized changes corresponding to tissues response to treatment, which may not be appreciable on visual inspection of volumetric or intensity changes. Additionally, different MRI protocols [Gd-T1, T2w, gradient echo sequence (GRE), fluid-attenuated inversion recovery (FLAIR)] are known to capture complementary diagnostic information regarding the patient's response to treatment; the utility of these MRI protocols has so far not been investigated to evaluate early and localized response to LITT treatment in the context of neuropathic cancer pain. In this work, we present the first attempt at (a) examining early treatment-related changes on a per-voxel basis via quantitative comparison of computer-extracted texture descriptors across pre- and post-LITT multiparametric (MP-MRI) (Gd-T1, T2w, GRE, FLAIR), subtle microarchitectural texture changes that may not be appreciable on original MR intensities or volumetric differences, and (b) investigating the efficacy of different MRI protocols in accurately capturing immediate post-treatment changes reflected (1) within and (2) outside the ablation zone. A retrospective cohort of four patient studies comprising pre- and immediate (24 h) post-LITT 3 Tesla Gd-T1, T2w, GRE, and FLAIR acquisitions was considered. Our quantitative approach first involved intensity standardization to allow for grayscale MR intensities acquired pre- and post-LITT to have a fixed tissue-specific meaning within the same imaging protocol, the same body region, and within the same patient. An affine registration was then performed on individual post-LITT MRI protocols to a reference MRI protocol pre-LITT. A total of 78 computerized texture features (co-occurrence matrix homogeneity, neighboring gray-level dependence matrix, Gabor) are then extracted from pre- and post-LITT MP-MRI on a per-voxel basis. Quantitative, voxelwise comparison of the changes in MRI texture features between pre- and post-LITT MRI indicate that (a) Gabor texture features at specific orientations were highly sensitive as well as specific in predicting subtle microarchitectural changes within and around the ablation zone pre- and post-LITT, (b) FLAIR was identified as the most sensitive MRI protocol in identifying early treatment changes yielding a normalized percentage change of 360% within the ablation zone relative to its pre-LITT value, and (c) GRE was identified as the most sensitive MRI protocol in quantifying changes outside the ablation zone post-LITT. Our preliminary results thus indicate potential for noninvasive computerized MP-MRI features over volumetric features in determining localized microarchitectural early focal treatment changes post-LITT for neuropathic cancer pain treatment. © 2015 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.2.4.041008]

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1 Introduction

It is estimated that 30% to 50% of all cancer patients undergoing some form of therapy, and 60% to 90% in advanced stages of cancer, suffer from intractable pain.¹ Neuroablative procedures targeting different pain centers have been investigated by neurosurgeons to alleviate the suffering of patients with intractable

cancer pain. One such recently investigated procedure is magnetic resonance image (MRI) guided laser interstitial thermal therapy (LITT)² that targets the cingulum (pain center in the brain) and has shown promise over existing treatment options, such as radio frequency (RF)-based ablation.³ A major advantage offered by LITT is its compatibility with MRI, allowing for high-resolution *in vivo* imaging to be used in LITT procedures.

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MRI is also capable of monitoring temperature change in the tissue, which enables real-time monitoring of LITT. More importantly, since LITT is based on thermal destruction of the target, it is not constrained by a maximum dose limit and may be used opportunistically multiple times post-treatment if required. The focused ablation via LITT may thus allow for a reintervention (after the initial treatment) in patients who do not respond favorably to the treatment either due to negative treatment effects (such as pain recurrence) or incomplete treatment. Accurately evaluating post-LITT changes via MRI may hence serve as an important step toward enabling early image-guided intervention and follow-up in neuropathic cancer pain patients who undergo LITT treatment.

Given how new LITT technology is for treatment of chronic cancer pain, currently, there does not exist any work on evaluating effects of LITT on the cingulum for pain management. However, in the context of evaluating treatment changes for neurological conditions, such as glioblastoma multiforme (GBM),^{4,5} patients are monitored qualitatively in a clinical setting via volumetric analysis on gadolinium-contrast T1-w (Gd-T1) MRI protocol.⁶ Gd-T1 allows for capture of volume of enhancement within ablation focus post-treatment, acquired at regular time intervals (24 h, 1 month, 3 months, and 6 months post-treatment) and comparing these changes with reference to pretreatment Gd-T1 to identify patients who may still be prone to treatment failure.⁶ LITT, however, being a localized treatment, introduces subtle, less-pronounced changes corresponding to the tissue's response to treatment. The volumetric analysis on Gd-T1 MRI, known as the MacDonald criterion,⁷ may hence be suboptimal in (1) precisely localizing specific LITT-related changes on MRI (since it involves evaluating a single volumetric parameter) and (2) employing complementary information to more sensitively and specifically capture treatment changes such as necrosis and edema that are better expressed on other MRI protocols [T2w and fluid-attenuated inversion recovery (FLAIR)]. The availability of MP-MRI protocols acquired post-LITT provides us with a unique opportunity to identify quantitative MRI markers that can reliably evaluate and monitor localized per-voxel changes across different MRI protocols post-LITT with respect to pre-LITT MRI. Early monitoring of MRI markers may additionally provide us with insights on immediate effects of LITT treatment and their role in predicting patients with successful treatment from patients who may have pain recurrence (established at 3 months post-LITT).⁸ There is hence a significant need for a quantitative approach that allows for evaluation and monitoring of voxel-level changes in imaging markers across multiparametric (MP)-MRI and identifies sensitive MRI markers that correspond to treatment changes post-LITT.

Over the last two decades, texture descriptors have shown utility in quantifying per-voxel microarchitectural information for computer-aided analysis for different disease and tumor types.⁹⁻¹¹ In this work, we explore the applicability of texture descriptors toward specifically addressing the following questions in the context of neuropathic cancer pain-management: (1) can texture descriptors with MP-MRI quantify early treatment related changes on cingulum for cancer pain-management that may not be appreciable via the McDonald criteria or visual inspection of original MRI? and (2) can we identify which MRI marker is more accurate in discerning early treatment related changes within and outside the ablation zone post-LITT?

Toward addressing these objectives, we present a quantitative approach (Fig. 1) for high-resolution (per-voxel) evaluation of early treatment-related changes *in vivo* on MP-MRI, via

1. *Registration of pre- and post-LITT MRI protocols:* Accurate coregistration of MRI protocols [Gd-T1, T2w, gradient echo sequence (GRE), FLAIR] is essential to quantitatively compare changes in imaging markers on voxel-by-voxel basis, across different protocols, while accurate coregistration of MRI markers pre- and post-LITT is required for careful monitoring of changes in MRI markers on a per-voxel basis. An affine coregistration scheme (linear transformation involving rotation, translation, scaling, and shear) was employed for alignment of different MRI protocols, as well as for pre- and post-LITT MRI for evaluating LITT response. Since LITT is a focal treatment, changes due to the treatment tend to be localized around the target of interest, and an affine coregistration scheme should be sufficient to align pre- and postimaging at different time points, instead of a sensitive nonrigid coregistration scheme (such as a basis-spline involving higher order nonlinear transformations to register images), which may lead to spurious coregistration.
2. *Correction of MR parameter drift:* One of the major drawbacks of MRI is known to be the lack of a quantifiable (tissue specific) interpretation of image intensities.¹² MR images taken for the same patient on the same scanner at different times are known to appear different from each other due to a variety of scanner-dependent variations; therefore, the absolute intensity values do not have a fixed meaning. The intensities thus need to be aligned pre- and post-treatment for a per-voxel comparison, so the MR images from different acquisitions have the same tissue-specific meaning. Pre- and post-LITT MR markers (T1-w, T2-w, GRE, and FLAIR intensities) were quantitated by correcting for intensity drift between acquisitions using intensity standardization developed by Madabhushi et al.¹² to ensure intensities, when compared on a per-voxel basis, that have the same tissue-specific meaning.
3. *Texture feature extraction on pre- and post-LITT MRI protocols:* Different MRI protocols (Gd-T1, T2w, GRE, FLAIR) were quantitated via raw intensity values as well as via computerized texture features. The feature extraction was performed on the intensity-corrected volumes (as described earlier). Texture features have previously demonstrated high effectiveness in disease characterization for different clinical applications.⁹⁻¹¹ Here, the texture features were computed on a per-voxel basis in order to examine their ability in accurately capturing LITT-related changes on post-LITT MRI (relative to pretreatment MRI) in patients with neuropathic cancer pain.
4. *Quantifying imaging changes on pre- and post-LITT MRI:* Normalized percent differences (relative to the pre-LITT values) were calculated between the pre- and post-LITT MRI features. This measure is extracted in order to quantitatively evaluate the sensitivity and the

specificity of different MRI features in (1) detecting increased changes within the ablation zone as a result of LITT, while (2) demonstrating little to no change within a spatially distinct normal region. Ideally, the MP-MRI parameter should demonstrate a large change within the ablation zone and small change within the normal region, as a result of treatment.

Our methodology (Fig. 1) is intended to provide a granular understanding of immediate imaging-related changes due to LITT *in vivo* in cancer pain patients who undergo LITT-based craniotomy. These findings may later enable early image-guided intervention in cases of unsuccessful or incomplete treatment, as determined by MRI-based markers of LITT-related changes.

The remainder of the paper is organized as follows: Sec. 2 describes previous related work in quantitative treatment evaluation. In Sec. 3, we provide methodological details of this work. Experimental results are presented in Sec. 4. We provide concluding remarks in Sec. 5.

2 Previous Work and Novel Contributions

Effects of cingulotomy via state-of-the-art RF treatment on cingulum have so far been studied in the context of pain-management and depression disorders.^{3,13} Yen et al.¹³ evaluated a total of 15 patients who were followed over time to identify signs of pain recurrence or no relief in patients who underwent RF-guided cingulotomy for pain management. Evaluation of a patient's response to treatment was performed at regular intervals (1 week, 3 months, and 6 months, and 1 year post-treatment). At the end point of evaluation (last available followup), nine patients had pain relief of more than 50%, six had pain relief between 25% and 50%, and seven had pain improvement of less than 25%. Similarly in Steele et al.,³ T2w MRI was used to evaluate the best location and volume of the lesions that are associated with a better clinical response for depression patients who underwent RF cingulotomy. The results suggested that patients when evaluated at 12-month followup had a superior clinical response associated with more anterior lesions with

Fig. 1 Flowchart showing different modules of our methodology. In step 1, registration across MRI protocols (Gd-T1, T2w, FLAIR, GRE), as well as across pre- and post-laser interstitial thermal therapy (LITT) is performed to bring all protocols to the same frame of reference (pre-LITT Gd-T1). Intensity standardization is then performed (Step 2) to ensure image intensities have the same tissue specific meaning across studies and acquisitions. Step 3 involves per-voxel texture feature extraction across pre- and post-LITT multiparametric (MP)-MRI. In Step 4, per-voxel imaging changes are quantified via difference maps both within and outside the ablation zone. Note that the red values correspond to high differences, while blue represents small differences in feature values across pre- and post-LITT MRI.

small volumes. The authors reported the best clinical response for patients with lesion volume of 1000 to 2000 cm³.

In the context of evaluating quantitative treatment changes post-treatment for other neurological applications, a recent focus has been on quantitatively monitoring changes in MP-MRI markers at different time points post-treatment during followup with respect to baseline (pretreatment) MRI. Khayal et al.¹⁴ investigated changes in diffusion parameters at pre-, mid-, and post-radiation therapy (RT) for postsurgical GBM patients to identify imaging markers that correspond to long-term patient survival. The results suggested that the changes in mid- to post-RT were significantly different between patients who progressed within 6 months versus those who were free of progression for 6 months after initiation of therapy. Similarly Foltz et al.¹⁵ evaluated short-term treatment response by evaluating changes in values of apparent diffusion coefficient and T2 relaxation every 2 weeks with respect to the baseline-MRI, over the course of 8 weeks. The significant findings of the work by Foltz et al. included (1) identifying MRI marker changes that were better correlated with treatment-related changes and (2) identifying an optimal timepoint since initiation of treatment, when recurrent disease resurfaced.

Our group^{8,16,17} has leveraged these qualitative characteristics within novel quantitative schemes for per-voxel evaluation and MRI signature construction to differentiate between possible radiation treatment outcomes (successful, unsuccessful, and recurrence). In our recent work,¹⁸ a fiducial driven based registration scheme was presented to evaluate LITT changes for GBM and epilepsy patients. Similarly, Viswanath et al.^{17,19} recently presented a quantitative approach via texture descriptors in conjunction with MP-MRI to evaluate post-LITT changes for prostate cancer. Texture descriptors were shown to outperform original MR intensities in identifying changes within the ablation zone, pre- and post-LITT. Litjens et al.,²⁰ similarly, presented a quantitative approach to distinguishing benign confounding treatment changes from residual prostate cancer on MRI following LITT, and Tiwari et al.^{8,21} developed a quantitative framework to monitor treatment changes over time on post-LITT MRI protocols in the context of epilepsy and GBM.

3 Methodology

3.1 Notation

We define $C_{\beta}^{\text{pre}} = (C, f_{\beta}^{\text{pre}})$ as the pre-LITT MR scene, where $\beta = \{\text{Gd} - \text{T1}, \text{T2w}, \text{GRE}, \text{FLAIR}\}$ corresponds to the different MR protocols and $f_{\beta}^{\text{pre}}(c)$ is the intensity value associated with every voxel c in a three-dimensional (3-D) grid C . C_{β}^{post} are the corresponding post-LITT MR scenes for every β , $\beta \in \{\text{T2w}, \text{Gd} - \text{T1}, \text{GRE}, \text{FLAIR}\}$ that have been aligned to C_{β}^{pre} . The region annotated as the ablation zone is denoted $A(C)$, while the normal, benign annotation is denoted as $N(C)$.

3.2 Inter- and Intraprotocol Registration of Pre- and Post-Laser Interstitial Thermal Therapy MRI

A 3-D affine transformation with 12 deg of freedom, encoding rotation, translation, shear, and scale, is implemented via the 3-D Slicer software 4.1²² to accurately align post-LITT MRI with reference to the pre-LITT Gd-T1 MRI volume, $C_{\text{Gd-T1}}^{\text{pre}}$, which yielded a registered 3-D volume, C_{β}^{post} , for every β , $\beta \in \{\text{Gd} - \text{T1}, \text{T2}, \text{GRE}, \text{FLAIR}\}$. During registration, the 3-D

volume is appropriately resampled and interpolated, in order to account for varying voxel sizes and resolutions between different protocols. Note that all MP-MRI acquisitions are aligned to the pretreatment frame of reference $C_{\text{Gd-T1}}^{\text{pre}}$ to enable quantitative comparisons [Fig. 1(b)].

3.3 Correction of MR Parameter Drift

When the image intensity distributions for $C_{\text{FLAIR}}^{\text{pre}}$ (red) and $C_{\text{FLAIR}}^{\text{post}}$ (black) were plotted together [Fig. 1(c)], it was clear that they were not in alignment, suggesting the presence of intensity drift (or nonstandardness)²³ between the pre- and post-LITT acquisitions. A similar trend was observed when plotting the distributions for $C_{\text{Gd-T1}}^{\text{pre}}$, $C_{\text{T2w}}^{\text{pre}}$, $C_{\text{GRE}}^{\text{pre}}$, and corresponding postimaging, implying the presence of drift in intensity values between pre- and postacquisitions. The algorithm¹² was implemented to automatically identify corresponding landmarks on each of the histograms and nonlinearly map them to one other. The mapping was calculated as a piecewise linear transform between corresponding intensity ranges on the histograms of the two acquisitions. As a result of intensity standardization, the histograms were aligned [Fig. 1(c)] and the MR intensities could be directly compared.

After segmentation of the lesion region of interest (ROI) on $C_{\text{Gd-T1}}^{\text{pre}}$, C_{β}^{pre} , and C_{β}^{post} , $\beta \in \{\text{Gd} - \text{T1}, \text{T2}, \text{GRE}, \text{FLAIR}\}$ are quantitated by correcting for intensity drift between acquisitions.²³ Correcting for this artifact thus enables quantitative comparison of the changes in MR intensities between pre- and post-LITT acquisitions, while ensuring tissue-specific meaning to the MR intensities being compared [Fig. 1(c)].

3.4 Texture Feature Extraction of Multiparametric MRI

A total of 78 texture features were extracted from each of C_{β}^{pre} , C_{β}^{post} , $\beta \in \{\text{Gd} - \text{T1}, \text{T2w}, \text{GRE}, \text{FLAIR}\}$ on a per-voxel basis. These features are obtained by (1) calculating responses to various filter operators and (2) computing gray-level intensity co-occurrence statistics Table 1, as follows:

1. Nonsteerable gradient features: A set of 17 nonsteerable gradient features were obtained via convolution with Sobel and Kirsch edge filters and first-order spatial derivative operators from each of C_{β}^{pre} and C_{β}^{post} .
2. Steerable gradient features: Gabor operators comprise the steerable class of gradient calculations, which attempt to match localized frequency characteristics.²⁴ A Gabor filter can be defined as the modulation of a complex sinusoid by a Gaussian function and is controlled by scale (λ) and orientation (θ) parameters. Forty-eight Gabor features were extracted from each of C_{β}^{pre} and C_{β}^{post} , via convolution with distinct Gabor operators obtained by varying each of the associated parameters.
3. Second-order statistical features: Second-order statistical features have been proposed by Haralick²⁵ and have found wide application in computing features with perceptual meaning for computerized detection systems.^{11,26} These features are based on quantifying the spatial gray-level co-occurrence within local neighborhoods around each pixel in an image, stored

Table 1 List of texture features employed in this work to evaluate early treatment response postlaser interstitial thermal therapy (LITT).

Modality	Feature set	Significance
T2w, Gd-T1, FLAIR, GRE	Nonsteerable gradient features	Detecting strength of horizontal, vertical, and diagonal edges within the image using linear kernels. ²⁶
	Steerable gradient features (Gabor features)	Convolving image with a Gabor filter bank, comprising filters with different frequencies and orientations.
	Second-order statistical features	Statistics of gray-level co-occurrence matrices such as angular second moment, contrast and difference entropy.

in the form of matrices. Thirteen Haralick features were calculated from each of C_{β}^{pre} and C_{β}^{post} , based on statistics derived from the corresponding co-occurrence matrices.

The reader is directed to Ref. 27 for a more detailed description of the individual texture features.

Feature extraction results in feature scenes $\mathcal{F}_{\varphi,\beta}^{\kappa} = (C, f_{\varphi,\beta}^{\kappa})$, where $f_{\varphi,\beta}^{\kappa}(c)$ is the feature value at location $c \in C$ when feature operator φ is applied to scene C_{β}^{κ} , $\kappa \in \{\text{pre}, \text{post}\}$, $\beta \in \{\text{Gd} - \text{T1}, \text{T2w}, \text{GRE}, \text{FLAIR}\}$. For ease of notation, the raw intensity values for every β were included in this set of feature scenes, i.e., there are a total of 79 feature scenes corresponding to each of C_{β}^{pre} , C_{β}^{post} , and $\beta \in \{\text{Gd} - \text{T1}, \text{T2w}, \text{GRE}, \text{FLAIR}\}$.

3.5 Quantifying Imaging Changes Due to Laser Interstitial Thermal Therapy

For each of $\mathcal{F}_{\varphi,\beta}^{\kappa}$, $\varphi \in \{1, \dots, 79\}$, $\kappa \in \{\text{pre}, \text{post}\}$, $\beta \in \{\text{Gd} - \text{T1}, \text{T2w}, \text{GRE}, \text{FLAIR}\}$, the range of values was normalized to have a mean of 0 and a mean absolute deviation of 1. This ensured that the different parameter values had a comparable range when quantifying differences between pre- and post-LITT MP-MRI.

Calculation of difference statistics was limited to voxels within the annotated regions $A(C)$ and $N(C)$. Due to the focal nature of LITT, it may be expected that regions within $A(C)$ will show large differences between pre- and post-LITT MP-MRI parameters, i.e., significant change due to treatment, while regions denoted by $N(C)$ show little to no change due to treatment.

The L_1 norm difference between a given pre- and post-LITT MP-MRI feature value can be calculated as

$$\delta_{\varphi,\beta}(c) = f_{\varphi,\beta}^{\text{pre}}(c) - f_{\varphi,\beta}^{\text{post}}(c) \quad (1)$$

for every voxel $c \in C$ (after normalization).

Difference scenes can be visualized within the ROI (ablation zone) by utilizing a color map, such that blue corresponds to

small difference values and red corresponds to areas of high differences. Therefore, regions annotated as $A(C)$ should be highlighted by red in the difference scene color map, which would correspond to large changes within the ablation zone due to successful ablation of the lesion focus. Along similar lines, regions annotated as $N(C)$ should be highlighted in blue in the difference scene color map, corresponding to little to no change in a region not targeted by focal laser ablation [Fig. 1(e)].

The normalized percentage change each of $\mathcal{F}_{\varphi,\beta}^{\text{post}}$ with respect to the corresponding $\mathcal{F}_{\varphi,\beta}^{\text{pre}}$, $\varphi \in \{1, \dots, 79\}$, $\beta \in \{\text{Gd} - \text{T1}, \text{T2w}, \text{GRE}, \text{FLAIR}\}$ was calculated as

$$\rho_{\varphi,\beta}^A = \text{MEDIAN}_{c \in A(C)} \frac{\delta_{\varphi,\beta}(c)}{f_{\varphi,\beta}^{\text{pre}}(c)}, \quad (2)$$

$$\rho_{\varphi,\beta}^N = \text{MEDIAN}_{c \in N(C)} \frac{\delta_{\varphi,\beta}(c)}{f_{\varphi,\beta}^{\text{pre}}(c)}, \quad (3)$$

where $\rho_{\varphi,\beta}^A$ and $\rho_{\varphi,\beta}^N$ quantify the change in MP-MRI parameter φ within the annotated regions $N(C)$ and $A(C)$ and are implicitly normalized between 0 and 1, where 1 corresponds to a large difference and 0 corresponds to no difference (between the pre- and post-LITT MRI feature). In an ideal scenario, we would expect that $\rho_{\varphi,\beta}^A$ will be close to or greater than 1, corresponding to a large change in the MP-MRI feature φ within the successfully ablated region (this would be considered a “highly sensitive” response). Similarly, $\rho_{\varphi,\beta}^N$ should ideally be close to 0, corresponding to no change in the MP-MRI feature φ within the normal region that should largely remain unaffected by focal ablation (implying a “highly specific” response).

3.6 Identifying the Most Sensitive and Specific Texture Descriptor in Capturing Laser Interstitial Thermal therapy Related Changes

Each MP-MRI feature was then ranked based on maximizing $\rho_{\varphi,\beta}^A$ while minimizing $\rho_{\varphi,\beta}^N$, $\varphi \in \{1, \dots, 79\}$, $\beta \in \{\text{Gd} - \text{T1}, \text{T2w}, \text{GRE}, \text{FLAIR}\}$, via the scoring function:

$$S(\rho_{\varphi,\beta}) = (\rho_{\varphi,\beta}^A)^2 - (\rho_{\varphi,\beta}^N)^2. \quad (4)$$

A high value for $S(\rho_{\varphi,\beta})$ will correspond to a feature that is highly sensitive (i.e., $\rho_{\varphi,\beta}^A$ close to 1) as well as highly specific (i.e., $\rho_{\varphi,\beta}^N$ close to 0).

4 Experimental Design and Results

4.1 Data Description

An Food and Drug Administration cleared surgical laser ablation system (Visualase Thermal Therapy System; Visualase, Inc., Houston, Texas) was employed for all LITT procedures. Details on available protocols for the four datasets are provided in Table 2. The datasets were collected as a part of an ongoing IRB approved study “Prospective and retrospective database review of magnetic resonance thermometry guided LITT” (under IRB protocol number 0220110296), at Robert Wood Johnson Hospital, New Jersey. Written consent was obtained from all patients for long-term followup. Secondary analysis

Table 2 Table demonstrating the available protocols for pre-LITT and post-LITT followup MRIs for the four-patient studies under evaluation.

Dataset	MRI follow-ups	MRI protocol	Treatment response
D₁	Pre-LITT 24-h Post-LITT	Gd-T1 Gd-T1	Successful
D₂	Pre-LITT 24-h Post-LITT	Gd-T1, T2w, GRE, FLAIR Gd-T1, GRE, FLAIR	Successful
D₃	Pre-LITT 24-h Post-LITT	Gd-T1, T2w, GRE, FLAIR Gd-T1, T2w, GRE, FLAIR	Successful
D₄	Pre-LITT 24-h Post-LITT	Gd-T1, T2w, GRE, FLAIR T2w, GRE, FLAIR	Failed

was performed on the anonymized data derived from data collected under informed consent. Since deidentified data were used for analysis, IRB consent was not required. Four intractable cancer pain patients were imaged 24-h post-LITT via MP-MRI (Gd-T1, T2w, GRE, and FLAIR) as a part of an ongoing study at Rutgers-RWJ Medical School between 2013 and 2014, after initial 3-Tesla MP-MRI. The patients were monitored up to 3 months after treatment. Three patients were found to be responders (*S*) to LITT treatment, while one patient had a failed treatment (*F*). Ground truth for responders and nonresponder to LITT was defined as substantial improvement in pain (>50% reduction in pain severity score and pain interference score²⁸) and little improvement (<50% reduction in pain severity score and pain interference score), established after 3 months post-LITT.

4.2 Annotations

Annotations of the ablation zone as well as the normal regions on post-LITT MRI were obtained via an expert neurosurgeon, who performed LITT surgery on these patients and with

substantial expertise in interpreting neuroimaging scans. Care was taken by the expert to ensure that the targeted ablation region during surgery was included in the annotated region of the ablation zone. Additionally, it was ensured that the ablation region and the normal regions are spatially distinct and of approximately the same volume, based on visual observation of intensities across the ablation zone and the normal regions, and on the same two-dimensional axial sections as that of the ablation zone.

4.3 Surgical Procedure

The details of the surgical procedure have been previously described.²⁹ Briefly, the procedure is performed in the following manner. The appropriate entry point and trajectory angle are identified using the Medtronic Stealth S7 (Medtronic, Inc., Minneapolis, Minnesota) using merged MRI and computed tomography images. A stab incision is made at the entry site, followed by the creation of a burr hole using a handheld 3.2-mm twist drill. The Visualase Thermal Therapy System (Visualase, Inc.) bone anchor is placed using the alignment rod and precision aiming device and then secured to the calvarium. The laser catheter is introduced through the fixed bone anchor. The laser used in the Visualase system is a 15-W, 980-nm diode laser, flexible diffusing tipped fiber optic, and 17-gauge internally cooled catheter. The patient is transferred to the MRI suite for the remainder of the procedure. In the MRI suite, the Visualase hardware system is connected to the MRI scanner, which allows for real-time thermal monitoring. The delivery of a test dose (typically, 3 W, 10 to 20 s) gives confirmation of laser placement. Safety margins are planned using the Visualase software such that the surrounding tissues temperatures do not surpass the predetermined limit (50°C) and the center of the lesion does not exceed 90°C (to avoid steam vaporization). In addition, the software allows for target temperature placement in multiple orthogonal planes if necessary based on the lesion location. Laser treatment is then started at the appropriate dose and duration to achieve maximal lesion destruction. During the ablation procedure, the software imports thermal imaging information every 5 s (for single-plane thermal imaging), allowing real-time analysis of the ablation process. There were no partial treatments in this series. Most patients were discharged within 24 to 36 h in the absence of complications or other general medical conditions.

Fig. 2 (a) Original FLAIR image, (b) and (c) show top two texture descriptors identified via $S(\rho_{\phi,\beta})$. Note the exaggerated response of texture descriptors around the ablation zone is more discernible in (b) and (c) as compared to (a).

4.4 Experiment 1: Evaluating MRI Markers in Quantifying Early Laser Interstitial Thermal Therapy-Related Changes Within and Outside Ablation Zone

Figure 2 shows the top two performing features, based on $S(\rho)$ for T2-FLAIR. Note the pronounced microarchitectural changes across the two texture descriptors [Figs. 2(b) and 2(c)] as

Table 3 Top three texture descriptors listed for T2-FLAIR, T2w, T2-GRE, and Gd-T1 MRI protocols.

MRI protocol	Texture descriptor	$S(\rho_{\phi,i})$ (%)
FLAIR	Gabor, $\Theta = 0.78, \Lambda = 11.31$	354%
	Gabor, $\Theta = 0.39, \Lambda = 22.62$	319%
	Gabor, $\Theta = 1.96, \Lambda = 11.31$	307%
T2w	Gabor, $\Theta = 1.96, \Lambda = 11.31$	141%
	Haralick information	126%
	Gabor, $\Theta = 2.35, \Lambda = 8.2$	110%
GRE	Gabor, $\Theta = 0.78, \Lambda = 11.31$	79%
	Gabor, $\Theta = 1.96, \Lambda = 11.31$	66%
	Gabor, $\Theta = 2.74, \Lambda = 11.31$	65%
Gd-T1	Gabor, $\Theta = 1.96, \Lambda = 8.2$	75%
	Gabor, $\Theta = 2.35, \Lambda = 5.65$	57%
	Gabor, $\Theta = 0, \Lambda = 22.62$	55%

Note: The bold text refers to the feature that was consistently identified as an important feature across the 4 MRI protocols.

compared to the original FLAIR image [Fig. 2(a)]. Table 3 summarizes the top three texture descriptors for Gd-T1, T2w, T2-GRE, and T2-FLAIR MRI ranked in descending order, along with the percentage change between pre- and post-LITT values within the ablation zone. It can be observed that Gabor responses were primarily ranked highest within each of the MP-MRI feature sets, based on a scoring function that attempted to maximize percentage change within the ablation zone while minimizing change within a normal region (between pre- and post-LITT MRI features). More specifically, Gabor features (at $\Theta = 1.96, \Lambda = 11.31$) were consistently identified as an important feature in evaluating treatment response across each of the different MRI protocols. This implies the presence of distinct microarchitectural orientation and gradient changes occurring specifically within the ablation zone as a result of LITT, possibly due to the presence of necrotic or ablated tissue in this region. However, normal regions show a markedly lower change in these features, likely because they are unaffected by the focal nature of LITT.

Figure 3 shows qualitative texture maps with (b) and (f) displaying an original FLAIR MRI image for a responder and a nonresponder patient, respectively, while (c) and (g) demonstrate corresponding best-performing Haralick, and (d) and (h) with best-performing Gabor features computed on a per-voxel basis for a responder and a nonresponder patient, respectively. Box-and-whisker plots of intensity and texture feature ranges across two responders and a nonresponder patient are shown in Fig. 4. Similarly, Fig. 5 shows 3-D scatter plots with median values obtained from top three features (Table 3) plotted across the x , y , and z axis, respectively, for all ablation zone slices from three patient studies (two responders, one nonresponder) for T2, and FLAIR protocols. Both the qualitative texture maps as well as quantitative plots seem to suggest that texture features accentuate the differences between responder and nonresponder patients and appear to better distinguish them as compared to original MR intensities on 24-h post-LITT MRI.

Fig. 3 Immediate post-LITT MRI for a nonresponder (a) and a responder (e) patient. Corresponding best performing Haralick and Gabor features are shown in (c)–(g) and (d)–(h), respectively. (b) and (f) Note the pronounced differences in Gabor and Haralick features as compared to original MR intensities.

Fig. 4 Box-and-whisker plots demonstrating a range of median values across slices for (a) FLAIR signal intensity and the corresponding top two texture features, (b) Gabor texture, $\Theta = 0.78$, $\Lambda = 11.31$, and (c) Gabor, $\Theta = 0.39$, $\Lambda = 22.62$ within the lesion area for a nonresponder and two responder patients. Similar results are shown in Figs. 4(d)–4(f) for (d) T2w signal intensity, (e) Gabor, $\Theta = 1.96$, $\Lambda = 11.31$, and (f) Haralick information computed with the lesion area. Note that the red line in the middle of each box reflects the median feature value while the box is bounded by 25th and 75th percentile of feature values. The texture features show a marked difference between the range of values across responder and non-responder patients as compared to original FLAIR and T2 intensity values.

Fig. 5 Three-dimensional scatter plots demonstrating median values plotted for top three texture features across x , y , and z axis, respectively, for different slices from three patient studies for (a) T2 and (b) FLAIR MRI protocols. Green triangles represent a nonresponder, while red circles represent responder patient studies.

Fig. 6 (a), (f), and (k) show pretreatment, while (b), (g), and (l) show post-treatment two-dimensional slice for T1-w, FLAIR, and GRE MRI, respectively. The corresponding intensity parametric maps are shown in (c), (h), and (m), and the top two features for each of T1-w, FLAIR, and GRE are shown in (d) and (e), (i), and (j), and (o) and (p).

4.5 Experiment 2: Relative Importance of MRI Protocols in Quantifying Laser Interstitial Thermal Therapy Changes Within and Outside Ablation Zone

Figure 6 shows the intensity parametric map along with top two features for each of T1-w, FLAIR, and GRE. Please note the

pronounced changes visible across the top two features for the three MRI protocols compared to original MRI intensities.

Figures 7(a)–7(d) show the barplot results of the top performing features in terms of quantifying treatment changes post-LITT for each of the different MR protocols, Gd-T1, GRE, T2w, and FLAIR, respectively. As apparent from Fig. 7, T2-FLAIR accentuated changes with a maximal normalized change

Fig. 7 Top 10 features for every MRI protocol, ranked in descending order based on $S(\rho_{\phi,\beta})$, $\beta \in \{\text{Gd} - \text{T1}, \text{T2w}, \text{GRE}, \text{FLAIR}\}$, i.e., showing a high change within the ablation regions and a low change within normal regions for (a) Gd-T1, (b) GRE, (c) T2w, and (d) FLAIR.

(350%) within the ablation zone (Table 3), followed by T2w with a maximal normalized change of 140% as compared to pre-LITT imaging, followed by Gd-T1 MRI and GRE. T2w and T2-FLAIR [suppresses cerebrospinal fluid (CSF) to improve contrast] sequences are known to accentuate the appearance of edema and assist in distinguishing edema from normal CSF.³⁰ T2-GRE was found to characterize a maximal normalized change of 79%, and Gd-T1 MRI was reported to capture 75% change in texture descriptors post-LITT. This suggests that FLAIR and T2w MRI may be able to better capture subtle early treatment-related changes (such as edema and swelling), as compared to T2-GRE and Gd-T1 MRI.

It is interesting to note that GRE was identified to be sensitive in identifying treatment changes within the normal areas (outside the ablation zone). GRE accentuated a change of 20% in the normal area outside the ablation zone, as compared to pre-LITT imaging. GRE is known to be sensitive to microhemorrhage (microbleeds) in the brain,³¹ and we believe is possibly quantifying acute effect of LITT to normal areas immediately after treatment. GRE was followed by Gd-T1, T2w, and FLAIR MRI in capturing treatment-related changes outside the ablation zone post-LITT.

5 Concluding Remarks

LITT holds tremendous potential as a minimally invasive treatment modality for pain management. However, a more widespread adoption of this new, exciting technique would involve rigorous quantitative evaluation of its treatment-related effects, which may be reflected via the changes in MRI markers post-LITT. Towards this end, we presented a novel approach via computer-extracted texture descriptors to evaluate early morphological changes post-LITT for chronic cancer pain patients. The motivation of this work was to identify texture descriptors that are associated with subtle microarchitectural changes (caused due to fundamental changes induced by LITT) that may not be discernible on the raw MR intensity images. We believe that the presented quantitative approach for evaluation of treatment-related changes between pre- and post-LITT MP-MRI may allow for the building of novel imaging-based prognostic indicators of patient treatment response. Our framework leveraged registration and feature extraction tools to accurately quantify treatment-related changes on a per-voxel basis on different MRI protocols. Our preliminary results based on four patient studies indicate the following:

- Computerized textural descriptors derived from MP-MRI had stronger association with early treatment-related changes than original MR intensities, evaluated on a voxel-by-voxel basis, within the ablation zone that were successfully ablated compared to normal regions.
- Gabor features (specifically at orientation, $\Theta = 1.96$, and wavelength, $\Lambda = 11.31$) are consistently identified as the highest ranked features for accurately quantifying LITT-related changes across all MRI protocols. These texture descriptors visualize responses across multiple scales, directions, and gradients and are possibly quantifying changes in microarchitectural glandular orientation specifically occurring within the ablation zone, as a result of fundamental changes in tissue architecture induced by LITT.

- FLAIR and T2w MRI identify to exaggerated early LITT effects within ablation zone, while GRE and T1-w MRI protocols exaggerated LITT effects outside the ablation zone.

While evaluated on a limited cohort of four patient studies from a single institution [University of Medicine and Dentistry (UMDNJ)] in the current study, our approach is intended to form a precursor to building of a novel imaging-based predictor of early focal treatment response to enable effective image-guided intervention for pain management. However, in the absence of a larger cohort of data and long-term follow-up MRI information, this work was limited to evaluating early treatment-related changes (edema and swelling) post-LITT. With the availability of a larger patient cohort and coupled with availability of post-treatment MRI, the framework presented in this paper is extensible to identifying computerized MR markers possibly associated with longer term treatment response. Such precise quantitative analysis could allow for planning of an early re-intervention in case the image predictor suggests that the initial intervention has not been successful. In future work, we plan to rigorously examine our registration module as well as the scoring function to obtain the most robust set of computerized MRI descriptors corresponding to early treatment failure on a larger patient cohort. Additionally, we plan to examine computerized MRI descriptors on follow-up MRI corresponding to delayed treatment related changes, such as thermal necrosis.

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