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Evaluation of Hepatic Tumor Response to Yttrium-90 Radioembolization Therapy using Texture Signatures Generated from Contrast-Enhanced CT Images

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Abstract

Rationale and Objectives—The aim of this study was to explore the use of texture features generated from liver computed tomographic (CT) datasets as potential image-based indicators of patient response to radioembolization (RE) with yttrium-90 (⁹⁰Y) resin microspheres, an emerging locoregional therapy for advanced-stage liver cancer.

Materials and Methods—Overall post-therapy survival and percent change in serologic tumor marker at three months post-therapy represent the primary clinical outcomes in this study. Thirty advanced-stage liver cancer cases (primary and metastatic) treated with RE over a three year period were included. Texture signatures for tumor regions, which were delineated to reveal boundaries with normal regions, were computed from pre-treatment contrast-enhanced liver CT studies and evaluated for their ability to classify patient serologic response and survival.

Results—A series of systematic leave-one-out cross-validation studies using soft-margin support vector machine (SVM) classifiers showed hepatic tumor texton and local binary pattern (LBP) signatures both achieve high accuracy (96%) in discriminating subjects in terms of their serologic response. The image-based indicators were also accurate in classifying subjects by survival status (80% and 93% accuracy for texton and LBP signatures, respectively).

Conclusions—Hepatic texture signatures generated from tumor regions on pre-treatment triphasic CT studies were highly accurate in differentiating among subjects in terms of serologic

response and survival. These image-based computational markers show promise as potential predictive tools in candidate evaluation for locoregional therapy such as RE.

Keywords

radioembolization; SIRT; liver cancer; CT; texture analysis

1. Introduction

Radioembolization with yttrium-90 (^{90}Y) microspheres (^{90}Y -RE) is an effective locoregional treatment for primary and metastatic cancers of the liver. This therapy is generally reserved for patients with advanced-stage liver cancer that is deemed not surgically resectable or that has failed to respond to standard chemotherapy [1]. Significant clinical benefit has been reported with radioembolization in both primary and metastatic cancers of the liver [1, 2], but it has also been observed that a subpopulation of patients undergoing radioembolization may exhibit disease progression. This disparity in response is currently not well understood.

Previous work has evaluated the influence of potentially indicative clinical features in colorectal cancer liver metastases such as tumor size, grade, and CEA level and found that these factors alone do not predict response to ^{90}Y -RE [1, 2]. One recent investigation identified several independent clinical factors including the presence of cancer-related symptoms, high hepatic tumor burden, and elevated bilirubin that may correlate with prognosis [3]. Another study developed a complex dosimetric model to predict metabolic response (expected changes on positron emission tomography (PET)) [4]. This model suggests a fairly accurate way of estimating response of individual tumors, but does not necessarily generalize to overall patient response. Given the high costs and potential risks associated with this therapy, there is a growing need to develop a set of robust prognostic tools to predict patient response to radioembolization.

Patterns of tumor heterogeneity may play a role in predicting patient response. Image *texture* signatures, which are quantitative measures of spatial patterns of image intensity, were chosen as the primary feature descriptors for malignant lesions in these studies because of their capacity to reliably generate objective, reproducible measurements of the inherent heterogeneity of the tumor environment. Texture features have been successfully implemented in numerous computer-driven applications, such as distinguishing among disease classes (e.g. hematologic malignancy subtypes [5], liver lesions [6], and a spectrum of other diagnostic applications). Recently, several research teams have begun to investigate the feasibility of using texture analysis methods for a wider range of applications extending beyond diagnostic purposes, including their potential use in improving prognostic accuracy [7, 8].

The work presented in this manuscript is a systematic study using texture-based computational markers to explore their capacity to reveal any potential correlation with patient response to radioembolization therapy. The computational markers utilized in these experiments were generated from hepatic tumor regions on triphasic CT. Two classes of 3D texture features were investigated: 1) texton histograms and 2) local binary patterns. Our study utilized a supervised learning approach to identify the accuracy with which these texture signatures could predict survival and stratify patients into specific response groups. Comparative performance is assessed using several clinical indicators of tumor response, including: a) overall survival (OS) and b) post-therapy changes in relevant serological tumor markers (TMChange). Throughout the course of these studies, we have followed guidelines

for research reporting standards of radioembolization in hepatic malignancies as outlined by the Interventional Oncology Task Force [9].

2. Materials and Methods

2.1. CT volume acquisition

This study utilized retrospective evaluation of a database of patients undergoing radioembolization over a three year period. This HIPAA-compliant study was performed under an approved Institutional Review Board protocol; informed consent was not required. The radioembolization cohort consisted of 30 patients with primary or metastatic advanced-stage liver cancer identified.

Standard-of-care triphasic CT scans of the liver with images reconstructed at 1.25-mm and 5-mm slice thickness were acquired one month prior to initialization of radioembolization therapy for pre-procedural planning. For the triphasic scan protocol, contrast was administered at a dose of 125 mL, 370 mg/mL at 4 cc per second through an upper extremity vein. Bolus tracking was used to initiate post-contrast imaging in the hepatic arterial phase when the aorta reached maximum attenuation, followed by a portal venous phase scan which was delayed 30 seconds after hepatic arterial imaging. Pre-procedural scans were de-identified and exported as DICOM images for subsequent image-based texture analysis.

2.2. Radioembolization therapy

Radioembolization treatment was applied as previously described [10]. To summarize, patient-specific ^{90}Y doses for radioembolization were calculated using the body surface area method [11]. The total dose was modified as recommended by the manufacturer based on the arteriovenous lung shunt fraction (determined by Technetium-99m macroaggregated albumin MAA-SPECT scan) and previous chemotherapy history. The determined dose was administered into the appropriate artery based on the type of treatment (whole liver or sequential bilobar) and patient-specific anatomy.

2.3. Clinical response outcomes

Overall survival (OS) was measured as the length of time in days between initiation of ^{90}Y radioembolization therapy and date of death. Serological tumor marker change (TMChange) was measured as the percent change over baseline in relevant tumor marker measured at three months post-therapy. The tumor markers utilized in this study represent standard clinical markers used to follow treatment response based on the histologic classification of the primary tumor. For example, carcinoembryonic antigen (CEA) was monitored for patients with colorectal carcinoma, alpha-fetoprotein (AFP) for hepatocellular carcinoma, and CA 27–29 for breast adenocarcinoma.

2.4. Semi-automated hepatic tumor segmentation

Tumor boundaries of one representative tumor from each subject ($n = 30$) were outlined on baseline contrast-enhanced CT imaging reconstructed at 1.25 mm slice thickness. Semi-automated axial contouring was performed on arterial phase CT images using livewire and levelset tools in the open-source software package MIPAV from the National Institutes of Health [12]. In cases where tumor boundaries were unclear on arterial phase but visible on venous phase, venous boundaries were used. Two-dimensional axial contours were used to generate three-dimensional voxel-wise masks via an intermediate mesh smoothing operation, which was developed using the Iso2mesh toolbox [13] for MATLAB [14] (2011a, The MathWorks, Natick, MA).

2.5. Texture Analysis

Figure 1 demonstrates an axial CT slice with a liver tumor present. Previous studies (e.g., [8, 15]) as well as unpublished observations have suggested that for these images, texture patterns may contain discriminative features for prediction of survival.

We calculated two sets of image-based texture features from the segmented 3D volumes: 1) texton histograms and 2) local binary patterns. These methods were selected specifically because of their intensity and scale invariance, as well as their focus on local patterns, which has contributed to well-documented applications in capturing fundamental texture elements in medical images [16–19].

Texton analysis identifies repetitive local textural microstructures that capture texture differences within the scope of human perception among a set of images. Textons have advantages over traditional texture measures in describing textures that contain high-level components. The use of textons to form a texton library for medical image texture analysis follows the approach described previously for histopathology specimens [5]. In this application, the LM Filter Bank [20] was used as the texton filter set. The LM filter bank is a set of first and second derivatives of 2D Gaussian functions at six orientations and three scales, coupled with eight Laplacian of Gaussian (LoG) and four Gaussian functions. The texton filter response feature vectors are used as appearance signatures of the representative liver tumor tissues. Multiscale LoG filtering has demonstrated success in emphasizing vascular features on liver CT [8] while reducing the effects of photon noise, which generally occur on a smaller scale [21]. After applying the LM filters to slices in three orthogonal planes, each voxel within the tumor volume is mapped to a 48-dimensional (48-*d*) space. Since the filter responses are inherently redundant, *k*-means clustering is applied to filter responses concatenated from several representative tumors. The *k*-means cluster centers form a texton library with $k_m = 100$ cluster centers selected as textons. A k_m -bin texton histogram is then generated for each tumor region, representing the frequency of voxels whose filter response is closest to each texton in the library. Finally, in order to focus on tumor heterogeneity and reduce the effect of size, the texton histogram is normalized to unity area. These experiments result in a 100-dimensional (100-*d*) texton signature for each lesion.

Local binary patterns (LBP), originally proposed by Ojala et al. [22] and later modified to a rotation and scale invariant approach [23], offer another approach to represent local texture within a set of images. In this study, LBP features were generated using a multi-scale approach with radius $r = \{1, 2, 4\}$ and number of neighbors $p = \{8, 12, 14\}$, respectively. Using rotation-invariant properties of the LBP operator, the number of possible decimal code patterns can be reduced to 10 for $r = 1$, 14 for $r = 2$, and 16 for $r = 4$. Feature images at each scale were generated based on the local intensity pattern at each voxel. A normalized LBP histogram is constructed for a complete tumor region using the frequency of voxels whose decimal code matches each rotation-invariant decimal code. Normalized histograms at all three scales are concatenated, resulting in a 40-dimensional (40-*d*) LBP feature signature for each lesion.

Tumor growth inherently spans three dimensions; therefore, any texture computations that only consider the axial dimension may miss important spatial patterns occurring in arbitrary directions across the transverse plane. For this study, texture analysis was applied to tumor volumes in an orthogonal space. The notion of texture in 3D space capturing more local information than 2D space has been proposed in previous work on CT images [24]. The method used in the present study consists of first generating a three-dimensional mask array, which specifies those CT voxels that lie within the tumor volume of interest (segmented using interactive contouring and mesh smoothing as described in Section 2.4). A schematic

of a CT volume sliced according to the three orthogonal planes is illustrated in Figure 2. Texton signatures representing each tumor in 3D space are then constructed by applying the filter banks in three orthogonal planes prior to texton library construction. The 3D LBP texture signatures are calculated in a similar fashion by concatenating histograms generated in each plane. The method presented here utilizes this strategy in order to capture some of the spatial variation that occurs in three dimensions without adding significant computational complexity.

2.6. Supervised Learning Experiments

Survival classification labels were applied to each case according to overall survival (OS) post-therapy relative to the median survival of 14 months ($I_i = 1$ if OS $\geq$ 14 months; $I_i = -1$ if OS $<$ 14 months). This timepoint represents the median survival for this cohort, splitting the N cases in half. Serologic classification labels were applied according to percent change in tumor marker ($I_i = 1$ if TMChange $<$ 0; $I_i = -1$ if TMChange $\geq$ 0).

2.6.1. Support vector machine classification—Tumor region texture signatures were classified using support vector machines (SVM) with radial basis function (RBF) kernel of the form $k(x_i, x_j) = e^{-\gamma \|x_i - x_j\|^2}$. SVM classification was implemented using the SVM-light package (SVM^{light} [25]). We used soft-margin SVM classification, which compensates for training errors (support vectors on the wrong side of the classifier) by imposing a penalty. For this small dataset, leave-one-out cross-validation was used for finding the soft-margin penalty parameter C and evaluation of the classifier performance.

2.7. Dimensionality Reduction

Due to the high number of dimensions in the texture feature representation of each lesion ($d_{\text{texton}} = 100$ and $d_{\text{LBP}} = 40$) compared to the number of cases samples ($n = 30$) as data points, several dimensionality reduction techniques, both linear and nonlinear types, were explored. Following a general framework for dimensionality, for a given set of real-valued feature vectors $x_i = \{x_1, \dots, x_n\}$, there exists a mapping T that can represent x_i in a lower-dimensional space governed by:

$$\hat{x}_i = T(x_i) + u_i, i=1, 2, \dots, n \quad (1)$$

where $u_i \in \mathbb{R}^d$ represents the sampling noise and $\hat{x}_i \in \mathbb{R}^d$ represents the feature vector x_i in the low-dimensional subspace. Depending on the nature of the dataset, the mapping T can be obtained by traditional linear techniques, such as principal component analysis (PCA), or by non-linear techniques, such as isometric feature mapping (ISOMAP) [26] and locally linear embedding (LLE) [27]. In this liver cohort, since we do not know *a priori* the nature of the underlying manifold from which we are sampling, we explore both linear and non-linear dimensionality reduction approaches. PCA is a method in which the mapping T_{PCA} represents linear combinations of the input vectors constructed to maximize the variance captured along each component in the reduced sub-space. The ISOMAP technique calculates a graph based on geodesic distances between points and then applies multi-dimensional scaling to the graph distances to obtain the low-dimensional mapping T_{ISOMAP} . LLE reconstructs the high-dimensional input points as linear combinations of their neighbors, thus preserving the local geodesic distance.

These experiments use a leave-one-out support vector machine (SVM) scheme for classification, which was implemented in the following procedure. The first subject was held out as a test case, and a SVM classifier was trained using the remaining $n - 1$ cases. The classifier was then used to predict the class for the held-out case. This procedure was repeated sequentially for each subject as a test case, and error rate was computed as the

overall percentage of incorrect matches between the classifier output (prediction) and the treatment outcome class (ground-truth).

3. Results

3.1. Patient Characteristics

The radioembolization cohort in this study included hepatocellular carcinoma ($n_{HC} = 1$), colorectal ($n_{CR} = 21$), breast ($n_{BR} = 3$), neuroendocrine ($n_{NE} = 1$), and other liver metastatic types ($n_{Other} = 4$). Patient characteristics are summarized in Table 1. The median number of treatments received per patient was 1.6. Two-thirds of subjects received sequential bilobar treatments and the remaining one-third received whole-liver treatment. Mean prescribed and mean administered activity infused were closely matched at 1.04 ± 0.40 GBq and 1.03 ± 0.43 GBq respectively. Median length of survival for the 30 cases considered in the preliminary dataset was 14 months from time of first radioembolization treatment date.

Of the thirty subjects analyzed in this study, the median percent change in tumor marker at three months post-therapy was +4.2%. Seventeen of thirty showed no change or increasing tumor markers and were labeled as serologic nonresponders. The remaining thirteen subjects were labeled as serologic responders.

3.2. Dimensionality Reduction and Classification

Initial experiments were performed using texton signatures on serologic response classification to determine the minimum number of reduced dimensions (d') that would give good classification results without yielding complex or overfitting classifiers. The results shown in Figure 3 indicated the lowest cross validation error (3.3%) using ISOMAP or PCA for dimensionality reduction with $d' = 5$ in the reduced dimensional space. When LLE was used, the lowest cross-validation error (30%) also occurred with the number of reduced dimensions at $d' = 5$. Based on these results, the number of dimensions was held constant at $d'_{texton} = 5$ for all remaining experiments with the texton signatures. Under similar experiments, the lowest cross validation error was identified for LBP signatures with $d'_{LBP} = 4$ and this dimension was used for all remaining experiments with the LBP signatures.

Support vector machines (SVMs) were applied with a radial basis function (RBF) kernel for classification, and leave-one-out cross-validation was used to evaluate the classification accuracy. Classification results using tumor texture signatures to distinguish subjects by survival are shown in Table 2. Classification results using tumor texture signatures to distinguish subjects by serologic response are shown in Table 3. Soft-margin SVM classification using a RBF kernel showed similar estimated performance for serologic response classification, with highest accuracy at 96.7% using texton signatures or LBP signatures. Estimated maximum performance for the texton signatures in distinguishing subjects by survival was 80% accuracy when reducing dimensions using ISOMAP. Survival classification using LBP signatures was estimated at 93.3% accuracy when reducing dimensions using either the PCA or ISOMAP techniques and lower accuracy (76.7%) using LLE for dimensionality reduction. LLE showed lower performance on this dataset in almost all classification tasks.

4. Discussion

Radioembolization remains continues to emerge as a promising locoregional therapy for primary and metastatic liver cancer [28]. While many patients respond favorably, progression of disease is observed in some patients. Prediction of outcome prior to treatment has the potential to spare some patients from exposure to the risks and high associated costs of therapy that is unlikely to prove beneficial in their cases. Our study approaches this

problem by evaluating texture-based computational signatures in predicting response to radioembolization therapy.

It has been suggested that tumor heterogeneity patterns may offer some insight in predicting patient response. For example, Alic et al. presented a recent study of image texture as a biomarker of treatment response in dynamic contrast-enhanced MRI [7]. In CT imaging, texture analysis provides a means to quantify the degree of heterogeneity in tissue density. A recent study by Miles et al. suggests a correlation between liver texture on CT images and survival in patients with hepatic colorectal metastases [8]. Since the texture exhibited within a given tumor region is an objective, reproducible description of the image-based characteristics of the diseased liver, we reasoned that tumor texture patterns might be indicative of therapy response outcomes. The present study was initiated to investigate whether tumor texture patterns might be useful in stratifying patients in terms of their most likely responses to radioembolization therapy.

Both of the methods used in this study, textons and local binary patterns, were chosen specifically based on properties of intensity and scale invariance, as well as a focus on local patterns, which has been documented in many medical image applications [16–19]. Texton-based analysis has been successfully implemented in many fields of texture-related research, including image classification [20], segmentation [29] and synthesis [30]. Local binary patterns (LBP) offer another scale- and also rotation-invariant representation of local texture within a set of images that has also demonstrated success in previous medical image applications for prediction of survival [17]. Thus, textons and LBP were utilized to characterize patterns of tumor texture heterogeneity in this liver cohort.

The classification results shown in Table 3 demonstrate that both types of texture signatures perform well in classifying by serologic tumor marker change in leave-one-out cross-validation experiments, with demonstrated accuracy as high as 96.7% and corresponding sensitivity and specificity at 100% and 93.3% for texton and LBP signatures respectively. While similar maximum performance was observed between the two types of texture signatures, some variability during the parameter selection stage was noted. The SVM soft-margin parameter C represents the cost of misclassifying points (essentially a tradeoff between finding the best fit for the data and maximizing the margin of separation), while σ represents the width of the radial basis function kernel. In comparing the two sets of texture signatures used in this study, the LBP signatures were very sensitive to the SVM hyperparameters C and σ , while the texton signatures were not as sensitive to the SVM parameters. This observation suggests that texton signatures may be more robust than LBP signatures when applied to future test data.

Previous investigations by Ganeshan et al. using whole-liver texture parameters to distinguish colorectal cancer patients by length of survival demonstrated 100% sensitivity and 65% specificity [15]. When compared with our method, which is applied directly to tumor regions rather than whole-liver, we demonstrate a shift in the sensitivity / specificity tradeoff, with lower sensitivity (80% for texton signatures and 93% for LBP signatures), but improved specificity (93% for texton signatures and 100% for LBP signatures). Higher specificity may be more desirable in our case, where the objective is to predict in advance which patients may exhibit shorter overall survival.

Both texture signatures show slightly less accurate performance in classifying survival beyond median compared to the serologic classification performance as demonstrated in Table 2. Texton signatures achieved 80% cross-validation accuracy with ISOMAP on the survival task but with low sensitivity (67%). LBP signatures achieved higher accuracy (93%) in distinguishing subjects by survival. The fact that the data exhibited better

separation by serologic classes than by survival classes supports the notion of a complex relationship between tumor heterogeneity and overall post-therapy survival. Patients identified as candidates for radioembolization are usually at an advanced stage of disease with varied chemotherapy and other treatment histories. Many patients undergo additional chemotherapy after radioembolization, which may have an effect on survival that is not distinctly attributable to their radioembolization [31]. Survival alone may not be a sufficient indicator to characterize response to radioembolization. Serologic tumor marker changes may also be limited as a sole descriptor of response. Thus, there is a growing need to better characterize response through the combined evaluation of temporal changes in clinical parameters (e.g., serologic tumor marker changes) and radiologic findings. Our team's future work will be targeted toward improved evaluation of response in this manner.

While we recognize that these preliminary feasibility studies utilized a relatively small number of subjects, the literature shows that radioembolization studies are often limited by sample size. This is due, in large part, because the treatment regimens are still undergoing testing in an attempt to gain a better understanding of safety requirements and potential applications. Other limitations of the study are its implementation in a single-institution series and application in a mixed population of primary and metastatic cancers. Encouraged by the results of these early feasibility studies, our team will continue to re-evaluate the use of image-based texture signatures as potential indicators of ⁹⁰Y-RE response using the growing cohort of patients leading to a larger representative sample.

The results of our efforts thus far show that the texture-based computational markers used in this study were useful in gauging response to therapy with yttrium-90 radioembolization in patients with advanced stage liver cancer. The high accuracy demonstrated here in classifying subjects in terms of serologic tumor marker response suggests that pre-procedural texture signatures from liver CT may be a useful tool for predicting patient response to radioembolization therapy.

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Figure 1. Representative liver CT axial slice showing tumor on arterial phase (left) and corresponding texture representations (right) using several scales of filter responses within the LM filter bank.

Figure 2. Schematic showing how tumor volume is divided into orthogonal anatomical planes for texture analysis.

Figure 3.

Error rate estimation for three different dimensionality reduction techniques as a function of number of reduced dimensions in distinguishing subjects by serologic response using texton signatures.

Table 1

Baseline patient characteristics

Demographics		Total (<i>n</i> = 30)
Age	65	9 (30%)
	< 65	21 (70%)
Gender	Male	16 (53%)
	Female	14 (47%)
Primary Diagnosis	Colorectal (CRC)	21 (70%)
	Breast (BR)	3 (10%)
	Neuroendocrine (NE)	1 (3%)
	Hepatocellular (HC)	1 (3%)
	Melanoma (MEL)	1 (3%)
	Other	3 (10%)
Treatment Cycles	2 (bilobar)	20 (67%)
	1 (whole liver)	10 (33%)

Table 2Texture signature performance in survival classification ($n = 30$)

Texture Signature	DR Method	Accuracy	Sens	Spec
Texton	PCA	66.7%	33.3%	93.3%
	ISOMAP	80.0%	66.7%	93.3%
	LLE	70.0%	53.3%	86.7%
LBP	PCA	93.3%	86.7%	100%
	ISOMAP	93.3%	86.7%	100%
	LLE	76.7%	73.3%	80.0%

Table 3Texture signature performance in serologic response classification ($n = 30$)

Texture Signature	DR Method	Accuracy	Sens	Spec
Texton	PCA	96.7%	100%	93.3%
	ISOMAP	96.7%	93.3%	100 %
	LLE	76.7%	80.0%	73.3%
LBP	PCA	96.7%	100%	93.3%
	ISOMAP	86.7%	86.7%	86.7%
	LLE	73.3%	86.7%	60.0%