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Uncertainty analysis of quantitative imaging features extracted from contrast-enhanced CT in lung tumors

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Abstract

Purpose—To assess the uncertainty of quantitative imaging features extracted from contrast-enhanced computed tomography (CT) scans of lung cancer patients in terms of the dependency on the time after contrast injection and the feature reproducibility between scans.

Methods—Eight patients underwent contrast-enhanced CT scans of lung tumors on two sessions 2–7 days apart. Each session included 6 CT scans of the same anatomy taken every 15 seconds, starting 50 seconds after contrast injection. Image features based on intensity histogram, co-occurrence matrix, neighborhood gray-tone difference matrix, run-length matrix, and geometric shape were extracted from the tumor for each scan. Spearman's correlation was used to examine the dependency of features on the time after contrast injection, with values over 0.50 considered time-dependent. Concordance correlation coefficients were calculated to examine the reproducibility of each feature between times of scans after contrast injection and between scanning sessions, with values greater than 0.90 considered reproducible.

Results—The features were found to have little dependency on the time between the contrast injection and the CT scan. Most features were reproducible between times of scans after contrast injection and between scanning sessions. Some features were more reproducible when they were extracted from a CT scan performed at a longer time after contrast injection.

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Conclusion—The quantitative imaging features tested here are mostly reproducible and show little dependency on the time after contrast injection.

Keywords

Quantitative imaging features; Texture; Contrast-enhanced CT; Lung

1. Introduction

In recent years, there has been a trend of developing quantitative imaging features or texture features to characterize tumors for the purposes of diagnosis, disease classification, and treatment outcome prediction [1–8]. This kind of research is also known as “Radiomics,” a high-throughput extraction of quantitative imaging features from medical images to create mineable databases for prognostic analysis [9, 10]. In Radiomics research, a large number of studies have focused on the texture features extracted from computed tomography (CT) images to predict the treatment outcomes of non-small cell lung cancer [1–3, 11]. These studies were based mostly on non-contrast diagnostic or pretreatment radiotherapy planning CT images. In diagnostic radiology, however, a large proportion of CT images are contrast-enhanced and texture features for these images have not yet been widely investigated. For example, perfusion CT imaging, one of the contrast-enhanced CT imaging protocols, has potential clinical oncology applications including assessments of treatment response, treatment stratification, and prognostication [12–15]. In the anticipation that quantitative imaging features will add prognostic value to contrast-enhanced CT, it is important to assess the uncertainty inherent to features extracted from these images [1, 16–18]. Specifically, the variability of texture features due to image acquisition parameters and the reproducibility of texture features across different scans should be investigated before these features are used for prognostic or predictive models. To the best of our knowledge, no previous studies have performed such uncertainty analyses for contrast-enhanced CT texture features.

In this study, we examined two important sources of uncertainty in CT texture features extracted from contrast CT studies. The first source of uncertainty is the potential dependency of texture features on the time between contrast injection and the CT scan; this amount of time could vary depending on the institution or the specifics of the examination. We developed a generic approach for the dependency check between texture features and time. The second source of uncertainty is the reproducibility of texture features across different scans. Reproducibility analysis helped to identify test-retest stable features for future prognostic analysis. Additionally, we examined the redundancy of the texture features, which could help build an optimized predictive model using compact prognostic features derived from the calculated redundant features.

2. Materials and Methods

2.A. Patient data

We retrospectively obtained patient data that had been collected under a perfusion CT protocol approved by the institutional review board. Eight patients undergoing perfusion CT scans on two sessions, 2–7 days apart, were enrolled into this study. These patients are metastatic lung cancer patients treated with either chemoradiation or radiation therapy. Each

of the patients had a single target that was larger than 2.5 cm when measured in the longest diameter. The target was a well demarcated contrast-enhancing solid mass. During our selection, we excluded patients who had cardiac and vascular pulsation artifacts in the target lesion and whose target lesion had been biopsied within 4 weeks or received radiation within 3 months prior to the perfusion CT scans.

The perfusion CT scans were obtained with the patient in the supine position on a 16-MDCT scanner (Light Speed, GE Healthcare) using a scanning protocol described in [12]. Each perfusion CT session comprised two phases: the “cine” scans and the “delayed” scans. The image data used for this study came from the “delayed” scans, which comprised six helical scans of the same anatomy at regular intervals. Each helical scan was obtained during an expiration breath-hold of approximately 7 seconds with 10 cm of craniocaudal coverage centered on the target lesion. The following parameters were used for each of the helical scans: tube voltage of 120 kVp, tube current of 90 mA, slice spacing of 3 mm, and field of view from 34 to 42 cm. The first helical scan started about 50 seconds after injection of 70 mL of a nonionic contrast agent at a rate of 7 mL/s, and the five subsequent helical scans were obtained every 15 seconds. Identical technical parameters were used for each patient in their two scanning sessions.

A total of twelve 3D helical CT scans were acquired for each patient, with 6 scans per session. For each patient, the lung tumor was manually delineated on the first scan of each session and propagated to each subsequent scan using deformable image registration [19]. The auto-propagated tumor contours were visually inspected and edited to correct any propagation errors.

2.B. Feature calculation

We calculated a variety of quantitative imaging features based on the delineated tumor for each 3D CT scan. As suggested by the previous studies [1, 2, 4], before the feature calculation, we applied lower and upper thresholds of -150 and 200 Hounsfield units to the tumor volume to exclude possible lung tissue, air, or bone to define the final tumor volume. A total of 122 features were extracted from the windowed tumor volume (Table 1). These features were organized into five categories according to the feature calculation method: intensity histogram (IHIST) [1, 20], co-occurrence matrix (COM) [21], neighborhood gray-tone difference matrix (NGTDM) [22], run length matrix (RLM) [23], and geometric shape [24, 25].

The IHIST features were calculated on the basis of intensity values or the histogram created from those values in the tumor volume. 256 bins were used for all features using a histogram for calculation. For the three local features of IHIST, a $9 \times 9 \times 9$ neighborhood region was used for the local entropy calculation and a $5 \times 5 \times 5$ neighborhood region was used for the local standard deviation and local range calculations. The maximum values of each calculation were used as the feature values. The IHIST features are related to the statistics of the intensity values of the tumor and may vary with the appearance of tumor. The COM, NGTDM, and RLM features were calculated from each slice of the tumor volume. These features are related to the spatial patterns of the tumor appearance. The COM keeps track of spatial relationships between intensity values. We calculated 4 directions (0° , 45° , 90° , and

135°) and 3 different offsets (1, 3, and 5) for each COM feature, and 256 levels were used in the COM calculation. The NGTDM is a one column matrix which tracks the average difference between voxels and their neighboring voxels. A 3×3 neighborhood region was used for the NGTDM calculations. The RLM keeps track of the frequencies of runs of different lengths for different intensities. We calculated 2 directions (horizontal and vertical) for each RLM feature. The geometric shape describes the geometric tumor characteristics based on the surface or shape of the tumor volume. Features in this category are related to the tumor size and the ways of how the tumor spreads out.

All feature calculations including pre-processing were performed using the Imaging Biomarker Explorer (IBEX) software [26]. IBEX is open-source software specifically designed for common quantitative imaging analysis tasks and is able to process multimodality image data for texture feature analysis including CT (contrast or non-contrast), CBCT, PET, and MR images. IBEX includes a variety of pre-processing algorithms such as thresholding and varied image smoothing filters. In addition, it enables user-specific feature algorithm development and predictive model design and promotes consistent data sharing between institutions. This software is freely available at http://bit.ly/IBEX_MDAnderson.

2.C. Time-dependent correlation analysis

We evaluated the time dependency of the features by examining the Spearman's correlation between the feature and the time after contrast injection. Spearman's correlation assesses how well the relationship between two variables can be described by a monotonic function [27]. For each feature in each scanning session, the Spearman's correlation between a vector of feature values calculated at 6 time points and a vector of the time after contrast injection in seconds, i.e. (50, 65, 80, 95, 110, 125), was computed for each patient, resulting in 16 correlation coefficients for each feature. Separately for each session, data from the 8 patients were pulled together and a Spearman's correlation was calculated to characterize each feature. Features with a coefficient greater than 0.5 were considered dependent on the time.

2.D. Reproducibility analysis

Concordance correlation coefficients (CCCs) [28] were used to quantify the reproducibility of a feature. As suggested by previous studies [18, 29], we defined reproducible features as those with a CCC > 0.9. We examined two types of reproducibility for the calculated features, time-dependent stability and inter-session stability, as shown in Fig. 1. We first examined the time-dependent stability. For each feature, the feature values obtained at the first scan for all patients in both scanning sessions constituted a vector. The CCCs were computed between this vector and that of each of the five subsequent scans. The average of these five CCCs was used to define the time-dependent stability for each feature. Next, we examined the inter-session stability. For each feature, the CCCs were calculated for each of the six helical scans in both scanning sessions. The CCCs at each time point and the average CCCs for all six scans were compared between the two scanning sessions.

2.E. Redundancy analysis

We used principal component analysis (PCA) [30] to evaluate the redundancy of the calculated features. PCA is a statistical procedure using an orthogonal transformation to convert possibly correlated features into linearly uncorrelated variables called principal components (PCs). If the features are redundant, a few PCs of large variance can be used to represent all of the features. These meaningful PCs compose a set of compact prognostic features that can be used for predictive models. The PCA was performed using a 122×96 matrix with each row representing a feature variable and each column representing an observation, i.e. one CT scan in one session for one patient. We analyzed the percentage of the total variance explained by each PC to identify a set of compact features. To exclude the case that a few features had much large variance, this process was repeated on the standardized feature values.

2.F. Impact of smoothing preprocess

For the same group of features, we applied an edge-preserving smoothing (EPS) filter [31] to the tumor volume before the feature calculation. The EPS is capable of preserving useful edge information while reducing the imaging noise (Fig. 2). Features calculated with EPS preprocess were compared with those calculated without smoothing in the aforementioned analyses to evaluate the impact of imaging noise to features.

3. Results

3.A. Time-dependent correlation analysis

The Spearman's correlation coefficients for each of the 122 features ranged from -0.20 to 0.25 (confidence intervals within $[-0.46, 0.50]$), implying that the features are not strongly dependent on the time between the contrast injection and the CT scan. We noticed that, for one particular patient, some features indeed showed a high correlation with the time; however, this correlation was incidental for this particular patient only because evaluation of all eight patients did not show an evident correlation. As an example, Fig. 3 illustrates the "10th percentile" feature as a function of time after contrast injection. The correlation coefficient for this feature was 0.07 , and the figure shows large variations in the feature values between patients.

3.B. Reproducibility analysis

The time-dependent stability is demonstrated in Fig. 4, which shows the percentages of the 122 features that have a certain CCC value or higher between Scan 1 and the five subsequent scans. In Fig. 4(a), the average of the 5 scans showed that 93.4% of the features had a CCC of 0.9 or greater, and the percentage of reproducible features for the 5 scans ranged from 92.6% to 95.9%. Scans 5 and 6 more quickly decreased in percentage of features with CCCs above a certain point as that point increased than the other scans, showing that those two scans were less reproducible from Scan 1 than the other scans were, indicating that some features were not stable along the time after contrast injection. The following features were not considered time-dependent stable: the three local features (local entropy max, local standard deviation max, and local range max) and the intensity range

(under IHIST), the correlation features at 90° (under COM), and the convex and orientation (under geometric shape).

Fig. 5 shows the percentages of the 122 features that have a certain CCC value or higher for inter-session stability analysis. In Fig. 5(a), the average of the 6 scans showed that 86.9% of the features have a CCC value of 0.9 or higher, indicating most features were reproducible between two scanning sessions. Also, the features obtained from Scan 6 (92.6% of features) were much more reproducible than those obtained from Scan 1 (73.8% of features), suggesting that some features gradually became more reproducible after contrast injection and eventually became stable. Of the 122 features, the three local features (local entropy max, local standard deviation max, and local range max) and the intensity range (under IHIST), most of the correlation features (under COM), and the convex and orientation (under geometric shape) were not identified as reproducible between scanning sessions. On the other hand, the following features showed increasing reproducibility as time after contrast injection increased: the global mean, percentile, and percentile area (under IHIST), the correlation features (under COM), the complexity (under NGTDM), the high gray level run emphasis and low gray level run emphasis (under RLM), and the convex and mean breadth (under geometric shape).

3.C. Redundancy analysis

The first 3 PCs explained 99.92% of the total variance in the 122 features obtained from the 96 scans, indicating a great deal of redundancy in the calculated features. These results suggest that 3 PCs could be used to compose a set of compact prognostic features for predictive models. This essentially reduced the size of feature matrix from 122×96 to 3×96, facilitating the creation of an effective model for prognostic analysis.

3.D. Impact of smoothing preprocess

We compared the aforementioned analyses of features calculated with and without EPS to understand the impact of imaging noise. There was no substantial difference between the time-dependent correlation analyses with and without EPS. The Spearman's correlation coefficients for all 122 features ranged from −0.15 to 0.25 when they were calculated with the EPS preprocess, similar to the range of −0.20 to 0.25 without EPS. For the reproducibility analysis, the results with EPS are shown in Fig. 4(b) for time-dependent stability and Fig. 5(b) for inter-session stability, respectively. Fig. 4(b) showed no substantial difference with addition of EPS but did show slightly improved time-dependent stability, with 95.1% of the features having a CCC of 0.9 or higher (in contrast to 93.4% without EPS). Fig. 5(b) showed that EPS had a substantial impact on the inter-session stability for Scans 1–4, but a much smaller impact for Scans 5 and 6, suggesting that the imaging noise had more impact before the texture features became stable. In the redundancy analysis, the first 3 PCs explained 98.33% of the total variance, again showing no substantial difference with the addition of EPS.

4. Discussion

We analyzed the uncertainties of quantitative imaging features extracted from contrast-enhanced CT images for lung tumors and found that the features had little dependency on the time between the contrast injection and the CT scan. Most of the commonly used texture features were reproducible between different scan times after contrast injection and between different scanning sessions several days apart. Some texture features appeared to change gradually after contrast injection but eventually became stable. These unstable features were more susceptible to imaging noise. In addition, we found great redundancy in the calculated features. PCA could be used to generate a set of compact prognostic features for predictive models.

This study investigated the uncertainty based on a limited number of texture features. It might not be complete, but the features were chosen from different categories and are commonly used features in many previous studies. Therefore, the results should be representative. Another limitation is that we did not investigate the impact of the amount of injected contrast agent. The CT-perfusion protocol used a constant amount of contrast, which prevented this study from investigating this question. In addition, it would be interesting to compare the texture features extracted from contrast and noncontrast CT images in terms of their reproducibility and stability. This will be the subject of a future study.

Quantitative imaging features have been widely used to characterize tumors for prognostic purposes. Researchers began to notice that the uncertainty of features extracted from a specific image modality should be thoroughly investigated before they were used for predictive analysis [1, 17, 32, 33]. Our study provides a comprehensive analysis of the uncertainties of texture features extracted from contrast-enhanced CT images so that these features can be used for prognostic analysis in the future. We suggest that users avoid using the unstable features identified in this study in their predictive models.

A limitation of this study is that we did not correlate the quantitative imaging features with pathologic information or clinical information. Treatment assessment or prognostication using these imaging features has not been investigated yet. However, the purpose of this study is to identify stable quantitative imaging features to be used for treatment outcome prediction. In the future, we will assess the identified stable features for prognostication.

Our study did not find evident dependency of any texture feature on the time between contrast injection and the CT scan; however, some texture features did change with time after contrast injection. This change might not be monotonic, which would explain why the time-dependent correlation analysis did not identify those features. The reproducibility analysis showed that some features extracted from a CT scan a longer time after contrast injection were more reproducible than those extracted from a scan a shorter time after contrast injection, indicating that those features become stable a sufficient time after contrast injection. Therefore, we suggest using the CT scan a sufficient time after the contrast injection (Scan 6 in our study) for texture analysis.

Redundancy analysis suggested a high correlation of the calculated features. Radiomics is a high-throughput process with a large amount of data, and, in general, the data have great redundancy. Therefore, we suggest performing PCA or other similar approaches to reduce the dimensionality of the calculated features and using the compact features to build an optimized prognostic model.

Our study found that preprocessing images with a smoothing filter had little impact on the texture features. The smoothing preprocess did change the reproducibility of the unstable features, however, the effect was minimized when the features became stable. We still suggest using smoothing preprocess when extracting texture features to minimize the impact from imaging noise, the level of which could differ between scanners. When a smoothing filter is used, it should not substantially change the underlying imaging features. A good choice may be the EPS filter used in our study.

In conclusion, most of the commonly used texture features extracted from contrast-enhanced CT scans for lung tumors are stable and reproducible across different times of scans and different patients and show little dependency on the time after contrast injection. These texture features could be used for prognostic analysis in the future.

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Highlights

- Quantitative imaging features had little dependency on the time after contrast injection.
- Most quantitative imaging features were reproducible between scanning sessions several days apart.
- Some texture features changed gradually after contrast injection but eventually became stable.
- Imaging noise had little impact on texture features.
- Compact prognostic features could be derived from calculated redundant features.

Figure 1.

Illustration of the reproducibility analysis performed in this study. The time-dependent stability evaluates the feature reproducibility between Scan1 and five subsequent scans after contrast injection and the inter-session stability evaluates the feature reproducibility between corresponding CT scans in two sessions.

Figure 2. The effects of edge-preserving smoothing filter applied to the tumor volume. (a) The original tumor volume and the encompassing contour; (b) the tumor volume after applying the edge-preserving smoothing.

Figure 3.

The 10th percentile feature values as a function of time after contrast injection for different patients. It shows large variations between different patients and large variations for some individual patients between different scanning sessions. The solid line represents Session 1 and the dashed line represents Session 2.

Figure 4. The percentage of features with a CCC greater than or equal to the indicated value for time-dependent stability analysis. (a) Features calculated without smoothing preprocess; (b) features calculated with EPS preprocess.

Figure 5.

The percentage of features with a CCC greater than or equal to the indicated value for inter-session stability analysis. (a) Features calculated without smoothing preprocess; (b) Features calculated with EPS preprocess.

Figure 6.

The percentage of the total variance of the data matrix explained by each principal component in the PCA.

Table 1

Quantitative imaging features and their categories used for this study. The number of features selected from each category was shown in bracket.

Intensity histogram (30)	Co-occurrence matrix (60)	Neighborhood gray-tone difference matrix (5)	Run length matrix (21)	Geometric shape (6)
Kurtosis	Contrast	Busyness	Gray level nonuniformity	Surface area
Skewness	Correlation	Coarseness	High gray level run emphasis	Convex
Range	Entropy	Complexity	Long run emphasis	Convex hull volume
Percentile (10th, 20th, ..., 90th)	Homogeneity	Contrast	Low gray level run emphasis	Mean breadth
Percentile area (10th, 20th, ..., 90th)		Texture strength	Run length nonuniformity	Orientation
Inter-quartile range			Run percentage	Roundness
Global entropy			Short run emphasis	
Global uniformity				
Global mean				
Global standard deviation				
Mean absolute deviation				
Local entropy max				
Local standard deviation max				
Local range max				