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Lung texture in serial thoracic CT scans: Correlation with radiologist-defined severity of acute changes following radiation therapy^a

Alexandra R. Cunliffe¹, Samuel G. Armato III, Ph.D.¹, Christopher Straus, M.D.¹, Renuka Malik, M.D.², and Hania A. Al-Hallaq, Ph.D.^{2,*}

¹Department of Radiology, The University of Chicago, 5758 S. Maryland Ave., MC9006, Chicago, IL 60637

²Department of Radiation & Cellular Oncology, The University of Chicago, 5841 S. Maryland Ave., MD2026, Chicago, IL 60637

Abstract

This study examines the correlation between the radiologist-defined severity of normal tissue damage following radiation therapy (RT) for lung cancer treatment and a set of mathematical descriptors of computed tomography (CT) scan texture (“texture features”). A pre-therapy CT scan and a post-therapy (median: 33 days) CT scan were retrospectively collected under IRB approval for each of 25 patients who underwent definitive RT (median dose: 66 Gy). Sixty regions of interest (ROIs) were automatically identified in the non-cancerous lung tissue of each post-therapy scan. A radiologist compared post-therapy scan ROIs with pre-therapy scans and categorized each as containing no abnormality, mild abnormality, moderate abnormality, or severe abnormality. Twenty texture features that characterize gray-level intensity, region morphology, and gray-level distribution were calculated in post-therapy scan ROIs and compared with anatomically matched ROIs in the pre-therapy scan. Linear regression and receiver operating characteristic (ROC) analysis were used to compare the percent feature value change (FV) between ROIs at each category of visible radiation damage. Most ROIs contained no (65%) or mild abnormality (30%). ROIs with moderate (3%) or severe (2%) abnormalities were observed in 9 patients. For 19 of 20 features, FV was significantly different among severity levels. For 12 features, significant differences were observed at every level. Compared with regions with no abnormalities, FV for these 12 features increased, on average, by 1.5%, 12%, and 30%, respectively, for mild, moderate, and severe abnormalities. Area under the ROC curve was largest when comparing FV in the highest severity level with the remaining three categories (mean AUC across features: 0.84). In conclusion, 19 features that characterized the severity of radiologic changes from pre-therapy scans were identified. These features may be used in future studies to quantify acute normal lung tissue damage following RT.

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*Corresponding author phone: (773)702-3309, fax: (773)834-7299, hal-hallaq@radonc.uchicago.edu.

Keywords

lung CT; texture feature analysis; deformable image registration

I. Introduction

Computed tomography (CT) scans are routinely acquired before and periodically after treatment with radiation therapy (RT) for lung cancer patients. These scans provide visual evidence of tumor response or regrowth and normal tissue damage, informing further clinical care. In approximately 50–100% of patients who receive lung cancer RT, radiologic evidence of normal tissue damage will develop.¹ These changes may appear as early as two weeks to three months following RT, often before symptomatic changes characteristic of radiation toxicities such as radiation pneumonitis (RP) occur.^{2,3} Past research indicates that early diagnosis and immediate treatment of RP leads to improved patient outcomes.⁴ These early radiologic changes thus have the potential to improve patient care by facilitating early detection of tissue damage typical of RP.

Several approaches have been developed to quantify lung tissue damage following RT, allowing for consistent, objective measurement of the extent of radiation injury.^{1,5} While these methods are based on mean lung CT density, radiation injury manifests through a number of different patterns including ground-glass opacification, diffuse consolidation, and scarring.⁶ To capture the complexity of these patterns, a higher-order set of measurements is required. One approach is to use texture analysis to distinguish among regions containing radiologic differences.

Texture analysis is a quantitative method to characterize image regions based on pixel values and the spatial relationships among pixels. Multiple groups have demonstrated the utility of texture analysis to quantify lung disease. Chabat et al.⁷ developed a technique to classify lung disease into three types (centrilobular emphysema, panlobular emphysema, and constrictive obliterative bronchiolitis). Uchiyama et al.⁸ and Uppalari et al.⁹ developed texture-based tools to identify and categorize lung disease patterns such as honeycombing and ground glass opacities. These methods, however, provide a measurement of lung disease at a single time point rather than site-specific evaluation of changes between serially acquired CT scans. Measurement of disease change between matched locations in scans becomes important when disease evolves non-uniformly due to localized treatment, as is the case with RT.

The present study investigated a method to quantify changes in normal lung tissue following RT for lung cancer. Texture changes between anatomically matched regions in scans acquired before and after RT are calculated and compared with the radiologist-identified severity of localized damage. The purpose of this study was to identify a set of texture features that correlated with the severity of normal tissue damage and to measure the severity-dependent magnitude of feature value change.

II. Methods

A. Patient Database

Twenty-six patients who underwent curative-intent RT for lung cancer at The University of Chicago Medicine between January 2007 and September 2011 were identified retrospectively under IRB approval (Table 1). One patient was disqualified because the post-therapy scan demonstrated lymphangitic spread of the tumor, impeding distinction of normal lung tissue from tumor tissue. All patients received curative levels of radiation dose (60 Gy) delivered using 6 MV or 6 and 18 MV photon beams. Patients received either three-dimensional conformal RT (n=22) or intensity modulated RT (n=3) while immobilized using custom alpha cradles. Treatment planning was performed using Pinnacle[®] 7.6, 8.0, or 9.0 (Philips Systems, Andover, MA) under the supervision of a radiation oncologist. All doses were calculated with correction for heterogeneous tissue density. Eligible patients were selected from over 100 lung cancer patients provided they had received two diagnostic-quality contrast-enhanced thoracic CT scans acquired (1) less than 6 months prior to the start of RT ("pre-therapy scan") and (2) less than 12 weeks following RT and, when applicable, before the diagnosis of RP ("post-therapy scan"). If multiple post-therapy scans were available, the earliest scan was selected. Scans were acquired after patients were instructed to inspire and hold their breath and reconstructed using identical high-resolution lung reconstruction and smoothing kernels. Additionally, patients had a gated or free-breathing treatment planning scan acquired without contrast enhancement and an associated dose map. Patients underwent routine clinical follow-up for at least eight months following the completion of RT to monitor for the development of RP.

B. ROI Identification

For all CT scans, semi-automated lung segmentation was performed by an experienced thoracic CT researcher [AC] using PinnacleR 9.0 model-based segmentation. Sixty ROIs distributed evenly among four dose levels (< 10 Gy, 10–30 Gy, 31–50 Gy, and >50 Gy) were randomly placed in each patient's post-therapy scan (Figure 1). To achieve this dose-level-based placement of ROIs in the post-therapy scan, demons deformable registration using Plastimatch v. 1.5.12-beta¹⁰ was performed to register each patient's treatment planning scan to their post-therapy scan; the resulting deformation vector field (DVF) provided a mapping between anatomically corresponding pixels in the post-therapy scan and the treatment planning scan (and hence the associated dose map). Next, non-overlapping 32×32-pixel ROI candidates were randomly identified in the segmented lungs of the post-therapy scan.¹¹ The center pixel of each ROI was mapped to the dose map using the DVF. An ROI of the same physical size centered at the mapped pixel location in the dose map was generated. The ROI was objectively assigned to one of the four dose levels provided that at least 75% of the area was contained within one particular level. Otherwise, the ROI was discarded. No portion of the ROI could overlap with the planned target volume (PTV), which had been contoured by a radiation oncologist during treatment planning. This process was repeated until 15 ROIs had been placed in each of the four dose levels.

C. Observer Study

A radiologist [CS] with over 15 years of experience assigned the 60 selected ROIs in each post-therapy scan to one of four categories (Level 1: “No visual evidence of interval abnormality”, Level 2: “Mild interval abnormality”, Level 3: “Moderate interval abnormality”, or Level 4: “Severe interval abnormality”) according to the severity of radiation damage captured within each ROI. A graphical user interface was developed for ROI categorization using Abras v.9.9b¹², a software package for medical image visualization and manipulation. The display enabled side-by-side viewing of pre- and post-therapy scans, allowing the radiologist to scroll through axial sections and alter the window/level settings. The interface allowed the radiologist to nudge an ROI in-plane by up to one-half of the ROI size (16 pixels, approximately 1 cm) to place it within a region of more uniform severity; ROIs could not be moved outside of the lung boundary or within the PTV boundary. No information was provided to the radiologist about a patient’s treatment plan, dose, or post-therapy toxicities.

D. ROI Mapping and Texture Analysis

Demons deformable registration was performed to register each patient’s pre-therapy scan to the post-therapy scan. The DVF formed through scan co-registration was used to map the center pixel of each post-therapy scan ROI to the pre-therapy scan. A 32×32-pixel ROI centered at the mapped center pixel was defined in the pre-therapy scan. This approach was based upon results of our previous work¹³, which showed that texture feature values demonstrated low variability when ROIs were mapped between diagnostic CT scans based upon the center pixel of the ROI. In addition, our previous results showed that utilizing 32×32-pixel ROIs compared with ROIs with matched physical dimensions decreased the bias in the measured texture differences. Twenty texture features distributed among first order, fractal, Laws’ filter, and gray level co-occurrence matrix (GLCM) feature classes were calculated in each of the 60 pairs of anatomically matched ROIs. These features were selected from among 140 features because of their stability in the absence of pathologic change.¹³ The percent change in feature value (FV) between each pre-therapy scan ROI and its corresponding post-therapy scan ROI was calculated for all 20 features according to the following formula:

$$\Delta FV = \frac{FV_{follow-up} - FV_{baseline}}{|FV_{baseline}|} \times 100\%$$

where $FV_{follow-up}$ and $FV_{baseline}$ represent the feature value calculated in the follow-up scan ROI and baseline scan ROI, respectively.

E. Statistical Analysis

Mixed effects regression using the lme4 package in R (v. 6.1.0) was performed to model FV as a function of the radiologist-assigned radiation damage severity level (fixed effect), allowing for patient-specific random effects. For each feature, an F-test determined if severity level had a significant effect on FV. The 95% confidence intervals on the model coefficients were measured with Markov Chain Monte Carlo sampling.¹⁴ Receiver operating

characteristic (ROC) analysis¹⁵ determined, for each feature, whether the various severity levels could be distinguished from each other based on FV. For each feature, the area under the ROC curve (AUC) was calculated using three binary comparisons: 1) severity level 1 versus levels 2–4, 2) severity levels 1–2 versus levels 3–4, and 3) severity levels 1–3 versus level 4. Paired Student's t-tests determined whether the mean AUC across features was significantly different among the three comparisons. To maintain model significance at $\alpha=0.05$, significance levels for individual tests were modified using the Bonferroni method, resulting in significance for p-values below 0.017 for each of the three tests.

III. Results

The radiologist assigned 1,500 ROIs in the post-therapy scans of 25 patients to one of the four severity levels (Figure 2) after manually nudging 64 ROIs (4%). Most ROIs contained no or mild evidence of interval abnormality (96%). Moderate or severe abnormalities were observed for nine patients. In some cases, a post-therapy scan ROI mapped to the pre-therapy scan extended beyond the lung boundary. These ROIs (n=81) were manually identified by the author [AC], who was blinded to the categorization assigned to each ROI, and excluded from further analysis. Table 2 shows the total number of ROIs in each severity level after these ROIs were excluded.

Regression modeling was performed for each of the 20 features. For 19 features (excluding GLCM entropy), FV was significantly related to differences in severity level. The changes in the regression model coefficients from level 1 are plotted in Figure 3. These values reflect the increase or decrease in FV for ROIs in levels 2–4 compared to level 1. FV either increased or decreased monotonically as severity level increased for all but three features (70% quantile, box-counting dimension, and GLCM entropy). For 12 features, significant differences between coefficients were observed at every level (Table 3). Compared with level 1, FV for these 12 features increased, on average, by 1.5%, 12%, and 30%, respectively, for levels 2–4.

The AUC values resulting from ROC analysis are displayed in Table 3. Mean AUC was significantly ($p<0.017$) lower when distinguishing ROIs in level 1 from levels 2–4 than for the remaining two comparisons. For the majority of features (15/20), the highest AUC value was achieved when distinguishing severity level 4 from levels 1–3.

IV. Discussion

This study demonstrated that lung tissue damage measured quantitatively by texture analysis correlates with the radiologic severity identified by an experienced radiologist. For most of the features considered, a significant increase or decrease in feature value change with increasing severity of damage was observed. Furthermore, the AUC for all features remained above 0.5, with mean AUC>0.75 for the majority of features, demonstrating the potential for these features to quantitatively assess the severity of radiation damage. Performance was lowest when separating regions with no abnormalities from the remaining 3 severity levels (Table 3) due to the subtle changes between “no abnormality” and “mild abnormality” regions (Figure 2). To determine how accurately regions with no interval abnormalities (Level 1) and mild abnormalities (Level 2) could be distinguished from one

another using FV, we also performed ROC analysis between these two levels only. AUC values ranged from 0.52 to 0.78 (mean: 0.67), decreasing by 0.03, on average, from the results achieved when regions with no abnormalities were distinguished from the other three severity levels together (Column 1 of Table 3). Though classification performance remained lower than the performance achieved when identifying regions with moderate or severe changes, these results indicate that regions containing mild abnormalities could still be identified through automated texture analysis.

In this study, only two-dimensional ROIs were considered due to the anisotropic voxel size, though extension of these methods into three dimensions warrants investigation. Xu et al.^{16,17} have demonstrated the potential for three-dimensional ROIs to improve classification of lung disease using texture analysis. Future studies could also benefit from combining features through an automated classifier, which would allow for a more robust measurement of the extent and severity of normal lung tissue damage following treatment. While texture analysis allows for quantitative characterization of CT scan appearance, other quantitative features such as ventilation-based measurements¹⁸ provide a measure of lung function following RT. Analysis of these features in combination with the texture features presented here could potentially improve automated identification and assessment of lung tissue damage.

Several groups have investigated mean CT density changes in lung tissue following RT. Ma et al.¹ measured a 75–200 Hounsfield unit (HU) increase in regional lung density in various dose regions of CT scans acquired 4–18 weeks following RT. Palma et al.⁵ observed correlation between density changes and the radiologist-determined severity of normal tissue damage, resulting in approximately 40 HU, 80 HU, and 150 HU average changes, respectively, in the peri-tumoral region of 3 month post-RT CT scans containing mild, moderate, and severe damage. The current study confirmed that mean CT density can assess the severity of post-therapy normal tissue damage; fitted coefficients for mean CT density were significantly different among the four severity levels, with a correspondingly high AUC (0.88). Mean CT density increased by 2%, 19%, and 54%, respectively, with increasing severity level, corresponding to an increase of approximately 15, 150, and 420 HU. Discrepancies between the density values in our study compared with Palma et al. may be attributed to differences in the treatment strategy, timing of posttherapy CT scan acquisition, and methods used to identify and categorize regions. The current study also incorporated features other than mean CT density that could characterize other patterns of normal tissue damage. Several of the features with the largest AUC values (i.e., median, 70% quantile, 30% quantile) are related to mean CT density and therefore would correlate highly with this feature and each other. Six of the 20 features, however, exhibited low correlation with mean CT density changes ($|r| < 0.5$), with four features exhibiting a negative relationship (i.e., FV decreased with increasing density). By measuring independent aspects of CT image texture, these higher-order features may serve in future studies to improve severity distinction among regions.

A minority of patients (36%) exhibited moderate and/or severe interval abnormalities in their post-therapy scans. The volume of the lungs that exhibited these changes was small; thus, the vast majority of ROIs contained no or mild change. Future studies should include

additional cases exhibiting moderate or severe changes post-therapy. Of the seven patients who later developed RP, only two had moderate and/or severe changes. In a study by Jenkins et al.¹⁹, 80% of patients diagnosed with RP after three-dimensional conformal RT had visual findings on their 3-month post-therapy CT scans. The scans in our study were acquired at a median time of one month post-therapy, which may explain the discrepancy in the rates of visual findings. To our knowledge, the present study is the first to focus solely on normal tissue changes prior to RP development.

One potential limitation is that intrinsic variability among patient treatment factors and CT scan acquisition parameters existed due to retrospective case selection. For example, differences existed among patient dose distributions and PTV size, the presence of pre-existing disease, and whether chemotherapy was administered, all of which may affect toxicities.^{20,21} In this preliminary study, the severity of radiation damage in each region was defined by a single radiologist. Past studies indicate only moderate levels of agreement between radiologists tasked with classifying various lung disease patterns.^{22,23} Discrepancies may therefore exist if ROIs were assigned by different radiologists to the various categories of radiation damage. In particular, regions with no or mild abnormalities may be inconsistently classified due to the subtlety of change (Figure 2), thus decreasing the ability to distinguish between the categories through texture analysis. Despite potential misclassifications, 12 features were identified that exhibited significant differences in FV among all four severity levels, indicating the feasibility of using texture analysis to quantify radiation damage. To further measure the effectiveness of this technique, future studies would benefit from having multiple radiologists to evaluate the level of consensus achieved regarding the severity of radiation damage in each region. Variations in the image acquisition parameters (e.g., exposure, pixel spacing, amount of intravenous contrast) and scanner models between pre- and post-therapy scans may also complicate measured texture differences. In part, these differences were considered during regression modeling by separating patient-specific feature value change between serial scans from changes due to severity level. Errors in the registration process may have led to incorrect identification of some matched ROIs in pre- and post-therapy scans. We observed in a previous study that, when the Plastimatch algorithm was used to deform serial CT scans acquired from lung cancer patients receiving RT, the mean registration error across patients was 2.4 mm in the absence of moderate or severe abnormalities and 4.6 mm in the presence of abnormalities.²⁴ In the current study, two patients visually demonstrated inferior registration compared with that of the other patients. To determine if the data from these poorly registered cases influenced the results of the study, analysis was repeated with these two patients excluded. The results of all statistical analyses, however, remained unchanged.

The approach outlined in this study could be applied in future research to quantitatively assess interventions intended to prevent radiation damage. For example, recent studies suggest that angiotensin-converting enzyme (ACE) inhibitors may protect normal lung tissue from radiation damage.^{25,26} Quantitative comparison of the post-therapy CT scans of patients administered ACE inhibitors with patients who did not receive the drug could test whether significant differences in normal tissue damage were present. The relationship between regional radiation dose and the severity of damage or feature value change also remains to be investigated. In the current study, 86% of regions that were classified as

containing moderate or severe abnormalities occurred in high-dose (>30 Gy) regions, indicating a relationship between dose and the severity of radiation-induced changes. Several groups have observed dose-dependence in the degree of lung tissue changes.^{1,27,28,29} A quantitative feature-based approach would allow observed radiologic changes to be correlated with local radiation dose. Analysis of the dose dependence of feature value change could also help measure patient-specific reaction to radiation therapy, facilitating individualized treatment for radiation-induced complications.

V. Conclusion

This study presents a texture analysis-based approach to characterize radiologic changes in lung tissue following RT. Nineteen texture features were identified that correlated with the radiologist-defined severity of normal lung tissue damage. In future studies, these features and methods could provide a quantitative measurement of the severity of acute damage in lung CT images following radiotherapy.

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Figure 1.

Flow chart describing the steps for automated identification of ROIs in a post-therapy scan using the dose map associated with a treatment planning scan.

Figure 2.

A random selection of post-therapy scan ROIs from a single patient that were assigned to each of the four categories by a radiologist. The matched pre-therapy scan ROI is shown above each post-therapy scan ROI.

Figure 3. Change in the fitted coefficients from Level 1 ("No visual evidence of interval abnormality") for all features in the four feature classes with 95% confidence intervals.

Table 1**Patient Characteristics and Image Acquisition Parameters**

Number of patients	25
	Male (n=9)
	Female (n=16)
Median patient age (range) [yr]	67 (48–84)
Number with smoking history	24
Lung cancer histology	NSCLC (n=18)
	SCLC (n=7)
Tumor location	Upper (n=19)
	Middle (n=2)
	Lower (n=4)
Number of patients who developed RP (grade 2 or higher)	7
Treatment regimen:	Concurrent chemo-RT (n=19)
	Sequential chemo-RT (n=3)
	RT only (n=3)
Median radiation dose (range) [Gy]	66 (60–70)
Dose per fraction [Gy]	2 (n=24)
	2.5 (n=1)
Mean PTV volume [cc] (range)	558 (90–1276)
Median time between pre-RT scan and RT start (range) [days]	17 (4–75)
Median time between RT end and post-RT scan (range) [days]	33 (2–82)
Treatment planning scan parameters (n=25):	
Peak kilovoltage [kVp]	120
Slice thickness/spacing [mm]	3
Mean pixel spacing (range) [mm]	1.08 (0.94–1.28)
Diagnostic scan parameters (n=50):	
Scanner type	Philips Brilliance 16 (n=8)
	Philips Brilliance 16P (n=21)
	Philips Brilliance 64 (n=21)
Peak kilovoltage [kVp]	120 (n=44)
	140 (n=6)
Peak kilovoltage difference between paired scans [kVp]	0 (n=23)
	20 (n=2)
Slice thickness/spacing [mm]	1
Mean exposure (range) [mAs]	233 (124–381)
Mean exposure difference between paired scans (range) [mAs]	46 (0–157)
Mean pixel spacing (range) [mm]	0.65 (0.51–0.83)

Mean pixel spacing difference between paired scans (range) [mm] 0.05 (0–0.18)

NSCLC: Non-small cell lung cancer

SCLC: Small cell lung cancer

RP: Radiation pneumonitis

RT: Radiation therapy

PTV: Planning target volume

Table 2

Distribution of ROIs in the post-therapy scans

Severity Level	Dose Region				TOTAL
	< 10 Gy	10–30 Gy	31–50 Gy	> 50 Gy	
Level 1	263	238	221	192	914
Level 2	86	115	119	125	445
Level 3	1	6	16	21	44
Level 4	0	1	1	14	16
TOTAL	350	360	357	352	1419

Table 3

AUC Values from ROC Analysis

Feature	Severity Level			Mean AUC
	1 vs. 2–4	1–2 vs. 3–4	1–3 vs. 4	
First-Order Features:				
Median	0.81	0.98	0.99	0.93
70% quantile	0.79	0.94	0.99	0.91
30% quantile	0.76	0.92	0.98	0.89
Unbinned entropy *	0.78	0.90	0.99	0.89
Mean *	0.77	0.89	0.99	0.88
Binned entropy *	0.72	0.90	0.98	0.87
5% quantile *	0.60	0.76	0.75	0.70
Minimum	0.54	0.66	0.68	0.62
GLCM Features:				
Sum average *	0.77	0.90	0.99	0.89
Sum of squares var. *	0.76	0.87	0.99	0.87
Sum entropy *	0.76	0.78	0.96	0.84
Difference entropy *	0.73	0.82	0.87	0.81
Entropy	0.63	0.74	0.63	0.67
Laws' Filter Features:				
R5L5 entropy *	0.68	0.80	0.88	0.78
S5L5 entropy *	0.65	0.80	0.85	0.77
E5L5 entropy *	0.67	0.82	0.63	0.71
W5L5 entropy *	0.66	0.79	0.61	0.69
Fractal Features:				
Brownian dim	0.55	0.78	0.82	0.72
Box-counting dim.	0.53	0.62	0.57	0.57
Fine box-counting dim.	0.52	0.53	0.57	0.54
Mean AUC (sd)	0.68 [†] (0.10)	0.81 (0.11)	0.84 (0.16)	

* Significant differences in regression model coefficients were observed among all levels.

[†] Mean AUC is significantly different from the mean AUC of either of the two other groups.