J of Nuclear Medicine Technology, first published online October 5, 2020 as doi:10.2967/jnmt.120.248393

Title: Pilot Study: Texture analysis of PET imaging demonstrates changes in 18F-FDG uptake of the brain after prophylactic cranial irradiation.

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Word Count: 3793.

Short Running Title: Texture, PET, cranial irradiation.

Abstract:

Rationale: Prophylactic cranial irradiation (PCI) is used to decrease the probability of developing brain metastases in patients with small cell lung cancer and has been linked to deleterious cognitive effects. While no well-established imaging markers for these effects exist, previous studies have shown that structural and metabolic changes of the brain can be detected with magnetic resonance imaging and positron emission tomography (PET). This study utilized an image processing technique called texture analysis to explore whether global changes in brain glucose metabolism could be characterized in PET images.

Methods: 18F-FDG PET images of the brain from patients with small cell lung cancer, obtained before and after the administration of PCI, were processed using texture analysis. Texture features were compared between the pre- and post-PCI images.

Results: Multiple texture features demonstrated statistically significant differences before and after PCI, when texture analysis was applied to the brain parenchyma as a whole. Regional differences were also seen but were not statistically significant.

Conclusions: Global changes in brain glucose metabolism occur after PCI and are detectable using advanced image processing techniques. These changes may reflect radiation-induced damage and thus may provide a novel method for studying radiation-induced cognitive impairment.

Key Words: texture analysis, PET, prophylactic cranial irradiation

Introduction:

Prophylactic cranial irradiation (PCI) is utilized in the treatment of patients with small cell lung carcinoma (SCLC) and has been shown to decrease the incidence of brain metastases and increase overall survival (*1,2*). However, there has been increasing understanding that PCI contributes to cognitive deficits in these patients, with 50-90% of adult patients who survive > 6 months after whole brain radiation experiencing deficits (*3*). These effects have been generally termed radiation-induced cognitive impairment.

Currently, there are no well-established imaging biomarkers for radiation-induced cognitive deficits. Based on posited theories for the etiology of radiation-induced cognitive impairment, it has been predicted that there will be roles for various implementations of magnetic resonance imaging (MRI) and positron emission tomography (PET) (*3*). A subsequent study has shown that MRI can detect significant changes in gray matter density and white matter microstructure in patients after receiving PCI (*4*).

Positron emission tomography with [18F]-2-deoxy-2-fluoro-D-glucose (18F-FDG) is currently used clinically for the evaluation of various dementias and cognitive impairment (*5,6*). The technique holds promise for delineating the effects of radiation-induced cognitive impairment based on its ability to demonstrate glucose metabolism in the brain, which is tightly coupled with neurosynaptic activity (*7*). Changes in 18F-FDG uptake in specific brain regions has been demonstrated in non-human primates receiving whole brain radiation (*8*), and a recent study showed that regional changes in 18F-FDG uptake could be detected in patients who underwent PCI (*9*). Since PCI treats the entire brain, it could also be expected that more global changes

would occur. A previous MRI study by Simo et. al. (*4*) demonstrated changes in white matter microstructure in the entire corpus callosum. It has not been previously explored whether advanced image analysis techniques are capable of detecting more global changes in 18F-FDG uptake in PCI patients.

Texture analysis in image processing is generally used to quantify the local variations in image brightness. Tied closely with the concept of tone, which describes the varying levels of image brightness, texture characterizes the spatial distribution of the tones in an image (*10*). Several techniques have been developed for texture analysis of images, which can be categorized into three groups: statistical, spectral, and structural methods. Statistical methods are based on analyzing the distribution of tones in an image by computing histograms and their properties such as statistical moments (*11*). These approaches are best suited to characterize features such as inhomogeneity, irregularity, and contrast. Spectral methods apply autocorrelation and Fourier analysis to evaluate periodic features of an image. Finally, structural approaches decompose the image into a set of sub-patterns, arranged according to certain placement rules. To date, there has been an abundance of work investigating the application of different texture analysis methods to volumetric medical imaging (*12*).

In recent years, a number of studies investigating the clinical value of using texture analysis to quantify PET uptake heterogeneity have been published. Most of this work is applied toward various tumor types (bone, lung, salivary, breast, head and neck, and brain cancer, among others) (*13,14,15,16*), as well as more recently toward the assessment of neurodegenerative diseases with PET (*17,18*). While these studies have shown much promise for differentiating malignant

from healthy tissue, little work has been focused on applying texture analysis to PET imaging within other contexts. We hypothesized that texture analysis could be applied to 18F-FDG PET imaging in order to detect changes in brain glucose metabolism after prophylactic cranial irradiation.

Materials and Methods:

Patient Selection:

This retrospective study was approved by the institutional Human Subjects Protection Program with a waiver of the requirement to obtain informed consent. Patients were selected from a data set previously generated by Eshgi et al. (*9*). In brief, those authors searched the institutional electronic medical record for patients with biopsy-proven small cell lung cancer (SCLC) who were treated with prophylactic cranial irradiation (PCI) between 2013 and 2016. Patients were treated between with PCI to a total dose of 2500cGy in 10 daily fractions of 250cGy fractions, typically delivered over two weeks. The target volume consisted of the entire brain and surrounding meninges within the cranium with beam flashing beyond skin with bottom of field either at foramen magnum or inferior to C1. Standard blocking of organs at risk such as lenses, pharynx, and oral cavity were achieved with multi-leaf collimation. All patients had previously been treated with first-line chemotherapy and thoracic radiation per standard of care. Patients with brain metastases or other intracranial pathology were excluded. These patients received 18F-FDG PET/CT imaging before and after PCI therapy as standard of care imaging for post chemoradiation tumor response. A total of 16 patients matched the inclusion criteria for this study. A single patient was excluded from the analysis as the result of poor image quality.

PET/CT Imaging:

18F-FDG PET/CT imaging was performed in accordance with standard institutional protocol. Patients fasted for a minimum of four hours and fingerstick blood glucose levels were measured prior to administration of 18F-FDG. Intravenous administration of 18F-FDG was performed at a weight-based dose of 3.7 MBq (0.1mCi)/kg, with a range of 185 MBq (5 mCi) to 370 MBq (10 mCi), after which patients sat quietly awake for approximately 60 minutes. Imaging was then performed from vertex to thighs using a GE Healthcare 690 time-of-flight PET/CT scanner. A low-dose CT scan was obtained with oral contrast and without intravenous contrast prior to PET acquisition. PET data was acquired using 7 – 8 bed positions, with 2.5 minutes per bed position. PET data was reconstructed using ordered subsets expectation maximization (28 subsets, 2 iterations).

Image Analysis:

The attenuation-corrected, time-of-flight PET image sequences were selected for use in this study. Slices including the brain from the vertex to the brainstem were manually selected. Manual segmentation of each slice was performed using ImageJ software in order to select only the patient's head and to exclude the background and the patient's arms. These segmented data were used to perform texture analysis of the entire brain parenchyma. Then, manual segmentation of the image sets was performed to isolate the right and left frontal, parietal, and temporal lobes. The occipital lobes were excluded from this analysis. Manual segmentation was performed by a radiology resident (DMS) with prior image segmentation experience. Texture analysis was performed within each brain region on the right and the left.

Texture Analysis:

The texture features were computed by first constructing and analyzing the Grey-Level Co-occurrence Matrix (GLCM). The GLCM was chosen over other texture analysis methodologies due to its widespread use and validation in prior literature and its ability to quantify pixel-scale variations in image brightness. Additionally, given that a manual segmentation method was used, having a robust feature set that is insensitive to individual pixel values was of interest to reduce the overall effect of any variability that may occur due to the manual segmentation procedure.

The GLCM is a spatial histogram that describes the distribution of grey-level values in an image occurring near one another (*10*). Each entry in the GLCM, $p(i,j \mid d, \theta)$, corresponds to the probability of a pixel (or voxel) with a grey-level of (i) being a distance (d) pixels away in the (θ) direction from a pixel with a grey-level of (j). With image data quantized into N_g grey levels, the GLCM is an N_g x N_g matrix. In this case, four directions for (θ) are possible: 0 degrees, 45 degrees, 90 degrees, and 135 degrees; for three-dimensional data, thirteen directions are possible for (θ). In this study, (d) is fixed at one pixel and the GLCM is computed for the four possible directions of theta for a single image slice. All images were normalized and quantized to 8-bit (intensity ranging between 0 and 255). From the GLCM, we then computed thirteen texture features introduced by Haralick et al (*10*), averaged over the thirteen directions for θ. Statistical significance for differences in texture features is computed using a two-way dependent student's t-test. The analyses were completed using the Python programming language on a computer with an Intel Core I-4710HQ CPU (2.50 GHz) and 16 GB DDR3L memory.

Results:

Global Differences in Texture Features:

Texture analysis was first applied to the whole brain segmented data set, with images including the entirety of the brain parenchyma from vertex to brainstem. Texture features were calculated for image sets pre- and post-PCI, and the results were compared.

Statistically significant decreases in four texture features were found after PCI: Contrast, Sum of Squares: Variance, Sum Variance, and Difference Entropy. Contrast decreased from 181.4 to 150.1 ($p = 0.043$), Sum of Squares: Variance from 0.1385 to 0.1203 ($p = 0.035$), Sum Variance from 8.479 to 8.303 ($p = 0.042$), and Difference Entropy from -0.563 to -0.595 ($p = 0.039$).

No statistically significant differences were found for Angular Second Moment, Correlation, Inverse Difference Moment, Sum Average, Sum Entropy, Entropy, Difference Variance, or Info. Measure of Corr. 1 or 2.

Results are summarized in Table 1.

Regional Differences in Texture Features:

Next, texture analysis was applied to the regionally segmented data set. Texture features were calculated for the right and left frontal, parietal, and occipital lobes both pre- and post-PCI. The texture feature results were then compared for each region in the pre- and post-PCI groups. The results of this analysis are detailed in Table 2. Statistically significant differences were found for

Sum Average in the right and left parietal lobes and for Info. Measure of Correlation 2 in the left parietal lobe.

However, given the performance of numerous (78) statistical tests in this analysis, a correction factor must be applied to the alpha (significance) level. Using the Bonferroni correction, an alpha value of $p < 0.00064$ would be required for definite statistical significance, which renders the regional differences in texture features nonsignificant.

Discussion:

This pilot study utilized texture analysis to explore changes in glucose metabolism in the brain after the administration of prophylactic cranial irradiation (PCI). The results demonstrate that statistically significant changes can be detected when image analysis is applied to the brain parenchyma as a whole. However, when the analysis was applied on a lobar regional basis, statistically significant differences were not seen. This suggests that texture analysis can characterize diffuse alterations in brain glucose metabolism occurring after PCI, a novel finding given that previous studies using 18F-FDG PET have shown only localized alterations (*8,9*).

Four texture features demonstrated statistically significant differences before and after PCI. Contrast measures the variations in brightness by providing higher weight to GLCM entries that are far from the diagonal. A high value for contrast is obtained when adjacent pixels have significantly different grey levels. Sum of Squares: Variance, or "joint variance," is calculated as the standard measure of variance for a distribution. In the context of texture analysis, it refers to the grey-level variability of a pair of adjacent pixels and is a measurement of image inhomogeneity. Unlike contrast, variance has no dependence on spatial frequency. A high variance is suggestive of a high contrast, but the converse does not necessarily hold true. Similarly, Sum Variance is a measure of variability, but measures the dispersion of the grey level sum distribution of the image. Difference entropy is a feature that is related to the amount of "disorder" related to the grey-level distribution in the image. More randomness in the image produces a higher level of entropy. Mathematical expressions for these four texture features are presented in Table 3.

In summary, all four of these texture features relate to randomness or variability in the image. All four features decreased significantly after PCI, indicating decreased variation in the 18F-FDG uptake. The underlying biochemical substrate for these alterations in glucose metabolism is unknown but could correlate with the widespread changes in gray matter density and white matter microstructure previously demonstrated using MRI (*4*).

This study is limited by small sample size, particularly in interpreting the regional analysis. Although there were trends toward differences in texture features in specific brain regions, the number of regions and texture features being tested required a strict high level of statistical significance. It is possible that significant regional differences in texture features could be detected with a larger data set. Another limitation exists in the use of manual segmentation of the image data, which could potentially introduce variability in the results. Developing an automated segmentation algorithm was outside the scope of this project. However, the texture analysis methodology used has an averaging effect over the pixels within the segmented volume. Therefore, variability in the boundaries of the segmented volumes should have had minimal effect on the ultimate computed feature values.

A potential confounder in these results is that each patient had also received first-line chemotherapy prior to PCI; however, this is unavoidable since it is standard of care. Several studies have documented both regional and global differences in 18F-FDG uptake in the brains of patients after receiving chemotherapy (*19,20,21,22*). Although the specific timing of the PET scans used in this study (pre- and post-PCI) increases confidence that the observed changes were due to PCI, it is possible that they may reflect a component of chemotherapy toxicity. It should

also be noted that none of the patient in this study received hippocampal-sparing radiotherapy (*23*), and as such these results cannot be generalized to that methodology.

Although this study focused only on a single texture analysis methodology in the form of the GLCM, further work could examine the application of other techniques (run length matrix, size zone matrix, and neighborhood gray tone difference matrix) in this context.

Unfortunately, this retrospective study was not able to collect neuropsychological testing data from the patients in order to quantify any cognitive deficits. Ideally, future work could perform longitudinal neuropsychological testing in conjunction with imaging to determine whether alterations in glucose metabolism in these patients corresponds to clinically significant cognitive impairment.

Conclusion:

This pilot study suggests that global alterations in glucose metabolism occur after prophylactic cranial irradiation, and that these changes can be detected using texture analysis techniques. Further work is needed to synergistically combine the global information from texture analyses with regional analyses of glucose metabolism. This combined imaging biomarker could then be used to augment neuropsychological testing for the study of radiation-induced cognitive impairment.

Disclosures:

David M. Sawyer: None.

Travis W. Sawyer: None.

Naghmehossadat Eshghi: None.

Charles Hsu: None.

Russell J. Hamilton: None.

Linda L. Garland: None.

Phillip H. Kuo: Consultant for Novartis, Konica Minolta, and Bayer. Consultant and speaker for Eisai, General Electric Healthcare. Grant funding from Blue Earth Diagnostics.

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Table 1. Texture analysis of whole brain segmented 18F-FDG PET data sets. P values refer to the probability of a statistically significant difference in each texture feature, when comparing the pre- and post-prophylactic cranial irradiation image sets.

Texture Feature	**P value**
Angular Second Moment	0.100
Contrast	0.043
Correlation	0.992
Sum of Squares: Variance	0.035
Inverse Difference Moment	0.168
Sum Average	0.963
Sum Variance	0.042
Sum Entropy	0.396
Entropy	0.229
Difference Variance	0.233
Difference Entropy	0.039
Info. Measure of Corr. 1	0.239
Info. Measure of Corr. 2	0.247

Table 2. Texture analysis of regionally segmented data sets. Values refer to the probability of a statistically significant difference in each texture feature (P value), when comparing the pre- and post-prophylactic cranial irradiation image sets.

Texture Feature	R Frontal	R Parietal	R Temporal	L Frontal	L Parietal	L Temporal
Angular Second Moment	0.292	0.212	0.173	0.449	0.176	0.335
Contrast	0.720	0.757	0.472	0.833	0.637	0.763
Correlation	0.821	0.232	0.557	0.984	0.609	0.989
Sum of Squares: Variance	0.651	0.630	0.483	0.850	0.384	0.740
Inverse Difference Moment	0.214	0.400	0.430	0.922	0.332	0.328
Sum Average	0.133	0.010	0.892	0.221	0.047	0.501
Sum Variance	0.618	0.416	0.557	0.884	0.351	0.760
Sum Entropy	0.478	0.205	0.576	0.846	0.744	0.296
Entropy	0.322	0.272	0.197	0.451	0.145	0.254
Difference Variance	0.286	0.238	0.842	0.852	0.550	0.351
Difference Entropy	0.452	0.437	0.790	0.953	0.785	0.574
Info. Measure of Corr. 1	0.465	0.448	0.790	0.478	0.138	0.409
Info. Measure of Corr. 2	0.921	0.980	0.061	0.497	0.034	0.109

Table 3. Relevant grey-Level Co-occurrence Matrix (GLCM) texture features, originally described by Haralick et al (10). $p(i,j|d,\theta)$ corresponds to the entry in the GLCM, designating the probability of a pixel with a grey-level of i being a distance d pixels away from a neighboring pixel with a grey-level of (j) in the (θ) direction. In this study, we fixed d at one pixel and averaged over the available directions for θ. N_g represents the number of grey levels. x and y are the row and column indices of the GLCM and $p_{x+y}(i)$is the probability of the two indices summing to $x+y$, whereas $p_{x-y}(i)$is the probability that the difference two indices is $x-y$; μ is the mean of p.

Feature Name	Formula
Contrast	$\sum_{n=0}^{N_g-1} n^2 \sum_{i=1}^{N_g}\sum_{j=1}^{N_g} p(i,j);\ n=\lvert i-j\rvert$
Sum of Squares: Variance	$\sum_{i}\sum_{j}(i-\mu)^2 p(i.j)$
Sum Variance	$\sum_{i=2}^{2N_g}(i-f_s)^2 p_{x+y}(i)$
Difference Entropy	$-\sum_{i=0}^{N_g-1} p_{x-y}(i)\log\left(p_{x-y}(i)\right)$