Original Article

Histogram Analysis and Heterogeneous Radial Changes Using ADC Map Images in Metastatic Brain Tumors for Dose Painting Intent

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Abstract

Background: Our goal in this study was to examine the heterogeneous radial changes within tumors using histogram analysis and determine whether this method could assist in the implementation of targeted radiation painting.

Materials and Methods: The diffusion-weighted imaging image data for 25 patients with primary lung cancer was examined. For patients with multiple metastases, the largest tumor diameter was considered, and three different radial categories were selected to assess heterogeneity changes. Finally, the histogram parameters of apparent diffusion coefficient (ADC) were compared among the 25 patients, and the *P* values were obtained using SPSS software to judge among results.

Results: The obtained outcome of our study demonstrated that in the central region of the tumor, up to a (0–0.3)r (tumor radius of the tumor), the tumor heterogeneity remains constant, and there is no significant difference in the ADC histogram percentiles of 25, 50, and 75. In the peripheral region of the tumor, at a distance away from the center, the heterogeneity level varies.

Conclusions: These findings indicate that this method has the potential to separate the boundary between the center of the tumor and its periphery in terms of the level of heterogeneity, which is one of the requirements of dose painting.

Keywords: Brain neoplasm, brain, diffusion-weighted imaging, dose escalation, malignant, metastases, neoplasms metastasis, radiotherapy, recurrent brain tumors

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Introduction

Cancer is one of the leading causes of death worldwide. It is estimated that by 2040, approximately 30 million new cases of cancer will be diagnosed.[1] Among the different types of tumors, brain tumors result in the loss of life for tens of thousands of individuals each year.[2] The most common malignant tumor within the skull is brain metastasis (BM). The likelihood of developing this type of tumor is 3–5 times higher compared to primary brain tumors.[3] Furthermore, around 8%–10% of cancer patients experience BM during the course of their disease.[2,4-6]

Certain cancers have the ability to metastasize to the brain, leading to BM. Lung cancer (20%–56% of patients), breast cancer (5%–20%), and melanoma (7%–16%) have a higher likelihood of causing such brain-related complications than

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other types of cancer.[3] The brain is recognized as the most frequent site for various cancer types.[7] Despite significant advancements in cancer treatment methods and the use of combination therapies, the complete prevention of treatment failure remains challenging in the majority of cases. One of the primary factors that contribute to the failure of treating malignant tumors is the occurrence of local recurrence after radiotherapy. The factors influencing local recurrence encompass pathological factors, such as tumor type and malignancy grade, as well as various radiobiological and physical factors.[8]

Among the physical reasons that contribute to local tumor recurrence, the following can be mentioned: inadequate dosage delivery in treatment, insufficient margin coverage for PTV (Planning target volume) during treatment planning, failure to adhere to an appropriate treatment protocol, incomplete success in surgical tumor removal, and errors in the execution of the treatment plan in the target area by the technician.[1] These factors can contribute to the local recurrence of the tumor through different cellular mechanisms in radiobiology, including cellular proliferation, various stages of angiogenesis, and the formation of small clusters of cancer cells within the tumor tissue, its surrounding vicinity, or even distant tissues.[9,10] In addition to pathobiological and physical factors, research has demonstrated that failure to consider heterogeneity among different regions of the primary tumor can also be a significant cause of recurrence. In other words, neglecting this factor can lead to the entire treatment target volume (PTV) being exposed to a uniformly prescribed dose.[11] In recent years, various treatment methods considering the heterogeneity within tumors have been utilized for tumor management. One of these approaches is the dose painting technique, which is employed to treat tumors with non-uniform doses in different regions. In this technique, a higher dose is selectively delivered to heterogeneous and radiation-resistant subvolumes within the tumor compared to other areas.[12,13]

The use of advanced biological imaging techniques, such as positron emission tomography (PET)-CT and MRI, enables us to determine the volumes and biological subvolumes within a tumor. These techniques are more effective in diagnosing the biology and behavior of tumors. Nowadays, there is increasing attention to the capabilities of various MRI images for simultaneous use. MRI images offer a wider range of high-resolution imaging sequences compared to other methods like CT and PET, providing us with unique, non-invasive insights into tumor heterogeneity.[14,15] Currently, multi-parametric MRI images are effectively utilized in dose-painting techniques for detecting tumor heterogeneity. However, this technique has some limitations. For instance, the methods for calculating and interpreting voxel values in multi-parametric images are not yet fully established, and these images require significant time and cost. Additionally, in some cases, the presence of motion and artifacts within the tumor environment can pose challenges in accurately determining the tumor status using this approach.[15,16] Recently, a new method called histogram analysis has been introduced to address such challenges in data collection and image analysis.[13] In the histogram analysis method, a function called a histogram is defined for each image, which determines the total number of pixels in the image and describes the statistical information present in the image using simple statistical methods.[13] This method involves analyzing the histogram using components such as the mean, standard deviation, maximum, and minimum thresholds.[17]

Histograms are more commonly used in imaging of extracranial regions in certain types of cancers, such as endometrial cancer (Woo *et al*., 2013),[18] renal cell carcinoma (Chandarana *et al*., 2012), uterine cervix cancer, and breast cancer (Johansen *et al*., 2009; Yuh *et al*., 2009).[15,19,20] In most studies, it is assumed that tumors grow radially.[21,22] In numerous clinical studies, the utilization of apparent diffusion coefficient (ADC) maps derived from diffusion-weighted imaging (DWI) in the region with the largest tumor diameter has been well documented. This technique is commonly employed in standard approaches like dose painting and histogram analysis, which utilize voxel intensity within the tumor to predict histological features and quantify tumor heterogeneity.[15,23] However, to the best of our knowledge, there is no research specifically examining radial changes in intertumoral heterogeneity using the histogram analysis method.

Materials and Methods

In a retrospective study, data from patients with BM from lung cancer who underwent MRI imaging was examined. The data spanned from December 1, 2021, to November 2, 2023. In total, images from 45 patients were included in this study. However, 20 patients were excluded for various reasons. The primary factor for excluding patients from the study was due to the absence of DWI and ADC images, which are important parameters of interest, and lastly, poor image quality.

Finally, after considering the remaining patients, a total of 25 individuals were considered in the study. This group consisted of 14 females and 11 males. Detailed information regarding these patients can be found in Table 1.

All patients underwent 1.5 Tesla MR imaging using a scanner system manufactured by Siemens in Avento, Germany. The imaging protocol consisted of T1-weighted images (TR/TE = 800/450 ms, slice thickness = 1 mm, and FOV = 250 mm). Additionally, DWI (b = 0 and 1000 s/mm^2) was performed for all patients as part of our MR imaging

Table 1: Characteristics of brain metastasis patient sample originated from lung cancer

Sex	Age	No. of patients	No. of brain lesions	Diameter
Male	57	11	1–3	2.9±0.72
Female	55	14	1–3	3±0.79

protocol for BM. The ADC values were automatically computed by the MR imaging device's operating console and presented as ADC maps. ADC histograms were generated with a bin of 1×10^{-5} mm^2/s and a range of $10–500 \times 10^{-6}$ mm^2/s.

In the specific study, only metastases with a radius equal to or greater than 2 ($2 \leq R$) were examined. These criteria were made for two main reasons. Firstly, using diameters smaller than this value could impede accurate co-registration with the ADC, potentially leading to incorrect results. Secondly, as the radial distance decreases, the accuracy and reliability of the study results decrease, reducing the likelihood of achieving the desired outcomes. For patients who had multiple metastases, the tumor with the largest diameter was considered.

To examine radial changes within the tumor, we divided tumor into central and peripheral regions based on three different radial intervals: (0-0.3)r and (0.3-1)r, (0-0.5)r and (0.5-1)r and (0-0.7)r and (0.7-1)r. Additionally, the entire region of interest (ROI) area was examined with a radius of r (0-1). Additionally, to illustrate that the analysis of graphs related to ADC map data can properly distinguish between different tissues, the tumor area was completely segmented from the surrounding normal tissue with a radius of r (0-1).

Then, using the Radiant Dicom software, ROIs were initially drawn on T1-weighted contrast-enhanced images. ROIs were co-registered to ADC maps via affine transformation with normalized mutual information as a cost function.

Among the desired percentiles for the histogram, the 25th, 50th, and 75th percentiles are the most important percentiles; however, the 75th percentile is a good balance to show the vast majority of measurements and is not affected by outliers. While not as stable as the median, the 75th percentile is a good choice for viewing medium to long-term trends. In this study, these three percentiles have been examined for review and comparison.

To generate the histogram parameters for ADC of these regions, for the 25th, 50th, and 75th percentiles, we utilized MATLAB software, version 2019, for programming purposes and the *P* values for these comparisons were obtained using the SPSS software.

Results

The obtained graphs of our mentioned process are illustrated in Figure 1 as a typical example of a case. In Table 2, regardless of the specified groups, we investigated the ROI region within the entire tumor and compared it with normal brain tissue. Within the distance range of (0-1)r within the tumor tissue, the 25th, 50th, and 75th percentiles had significant differences with values of (459–33), (470–78), and (483–57), respectively. This emphasizes the existence of heterogeneity in different radii of tumors. Instead, considering the similar values of (238–48), (249–46), and (258–50), which correspond to the 75th, 50th, and 25th percentiles of normal tissue, there were no significant differences between the data, according to *P* value results, which was predictable in normal tissue homogeneity.

In Table 3, the data analysis between the central and peripheral parts of the tumor, in all percentiles, showed no significant variations when the radius ratio of these two areas was the same ((0-0.5)r). Upon examining these values, for the central radii range of ((0-0.3)r) and (0-0.7)r), significant differences were observed among them. For the central part of the tumor with a radii range of ((0-0.3)r, all percentiles confirm our claim. However, for ((0-0.7)r, only 25th and 75th percentile support our idea.

Discussion

In recent years, the technique of dose painting has gained significant attention as a therapeutic approach for heterogeneous regions within tumors. The primary objective of this technique is to deliver non-uniform doses to the heterogeneous regions within the tumor. However, identifying these regions requires the use of costly functional imaging techniques. In this study, we investigated the hypothesis that analyzing ADC map MRI images can provide information about the heterogeneous changes within the tumor. Therefore, utilizing this technique becomes more convenient, efficient, and cost-effective.

We conducted a radial analysis to examine the changes within the tumor. After reviewing studies conducted on BMs, up until the time of this research, no study was found that specifically

Table 2: Comparison of different percentiles between tumor and normal tissue

	Tumor	Normal tissue	*P*
25th percentile ($\times 10^{-6}$ mm^2) (x-y)	(459, 30±9.7)	(238, 48 8.67)	0.045
50th percentile ($\times 10^{-6}$ mm^2) (x-y)	(470, 78±6.98)	(249, 46 8.34)	0.015
75th percentile ($\times 10^{-6}$ mm^2) (x-y)	(483, 57±4.67)	(258, 50 5.82)	0.049
P	0.001	0.221	

Table 3: 25th, 50th, and 75th percentile values for the study groups

	Central	Peripheral	*P*
25th percentile ($\times 10^{-6}$ mm^2)(x-y)	(0-0.3)r (460, 7±1.124)	(0.3-1)r (459, 45±10.34)	0.002
	(0-0.5)r (465, 21±6.31)	(0.5-1)r (455, 20±3.47)	0.425
	(0-0.7)r (463, 42±11.45)	(0.7-1)r (426, 6±0.345)	0.034
50th percentile ($\times 10^{-6}$ mm^2)(x-y)	(0-0.3)r (470, 10±5.67)	(0.3-1)r (471, 56±8.98)	0.005
	(0-0.5)r (471, 31±5.67)	(0.5-1)r (470, 40±9.56)	0.345
	(0-0.7)r (472, 40±6.45)	(0.7-1)r (467, 22±11.21)	0.078
75th percentile ($\times 10^{-6}$ mm^2)(x-y))	(0-0.3)r (478,10±0.89)	(0.3-1)r (483, 46±1.78)	0.050
	(0-0.5)r (475, 23±2.33)	(0.5-1)r (485, 35±4.23)	0.123
	(0-0.7)r (482, 49±6.34)	(0.7-1)r (483, 16±1.34)	0.003

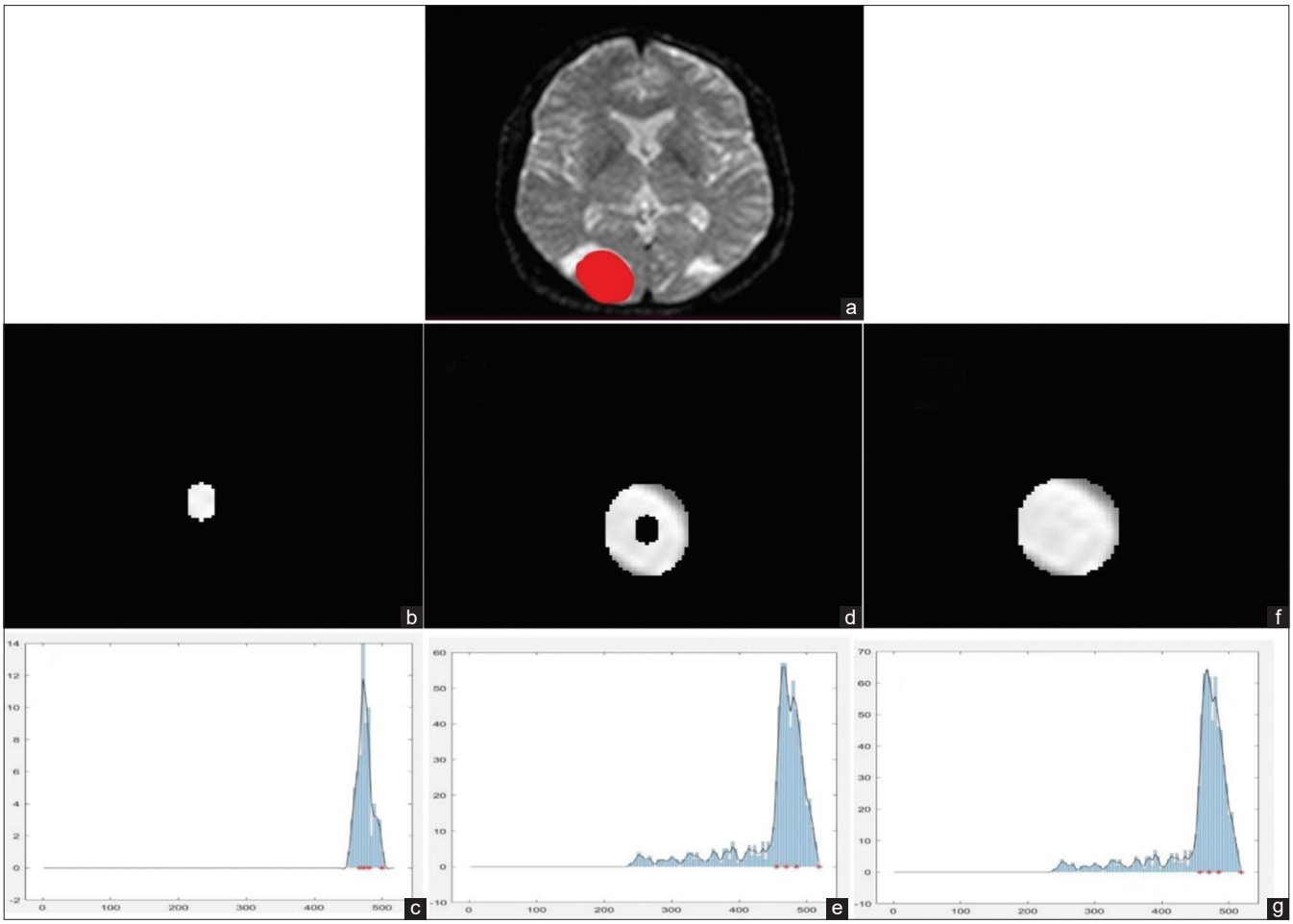


Figure 1: Processing workflow diagram. (a) contrast-enhanced T1-weighted MR image with the ROI of the entire BM overlaid (b) the central region of the tumor, (c) histogram of the central region of the tumor, (d) the peripheral region of the tumor, (e) histogram of the peripheral region of the tumor (f) the entire tumor, (g) histogram of the entire tumor

investigated the radial changes in tumor heterogeneity using a histogram. To examine the heterogeneity, we analyzed the changes within the tumor in a radial manner.

Numerous studies have been conducted on the relationship between DWI parameters in BMs and cancer biomarkers.[24-26] The main focus of these studies has been to determine whether DWI parameters can accurately predict patient outcomes. Additionally, another category of studies has explored and evaluated histograms to provide relevant information for tumor prognosis.[24] However, we were unable to find any articles specifically addressing the radial changes within heterogeneity using histograms.

Our study results have shown that in the central region of the tumor, up to a distance of (0-0.3)r, the level of tumor heterogeneity remains constant and does not change with an increase in the radius. This finding indicates that significant changes in heterogeneity do not occur within this distance, and the distribution of cells in this region of the tumor is relatively uniform. However, in the peripheral region of the tumor, at a distance from the center, the level of heterogeneity varies. These results indicate that tumor heterogeneity is dependent on the distance from the center and the diameter of the tumor. The implementation of the dose-painting technique with this method requires more investigation.

In general, On smaller radii, the degree of heterogeneity is higher than the tumor margin. This increase is more noticeable at the 25th and 50th percentiles, indicating the presence of significant variations in heterogeneity at these points. This result may be due to the increasing distance from the tumor center and the proximity to regions of the tumor where the contribution of healthy cells in that area is higher.

This study effectively demonstrated that, even in an apparently homogeneous tumor, there are regions of heterogeneity. These findings suggest that the method employed in this study could be targeted for further investigations into additional dose painting. To validate this model, it would be advisable to compare the results with a by-number approach.

Conclusion

Based on the findings, it was observed that there is detectable heterogeneity in the tumor volume, which may be attributed

to various factors such as hypoxia, genetic factors, and hemorrhage. However, no heterogeneity was observed in normal tissue; in fact, there is more uniformity.

At first glance, it may seem like a simple investigation, but in reality, it is an innovative approach, and by identifying and addressing weaknesses and issues, more accurate and comprehensive results can be achieved.

Our challenges in this study include the following main factors. Despite having a sufficient number of patients for the study, the expansion of the patient population enables us to examine a broader and more diverse sample from the target population. Consequently, this has the potential to enhance the quality and robustness of our findings in this specific study. Furthermore, it is advisable to conduct additional research on histogram parameters to enhance the accuracy of the study. Lastly, to achieve a more precise evaluation it is recommended to perform this analysis on patients with brain tumors of different primary origin, accompanied by pertinent pathological information.

It is also recommended to compare the results of this method with other image processing methods.

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Conflicts of interest

There are no conflicts of interest.

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