Statistical analysis of radiomic features in differentiation of glioma grades

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Abstract

Radiomics is an important quantitative feature extraction tool used in many areas such as image processing and computer-aided diagnosis. In this study, the discriminability of brain cancer tumour grades (Grade II and Grade III) with radiomic features were analysed statistically. The data set consists of 121 patients, 77 patients with Grade II tumours and 44 patients with Grade III tumours. A total of 107 radiomic features were extracted, including three groups of radiomic features such as morphological, first-order and texture. Relationships between the characteristics of each group were tested by Spearman's correlation analysis. Differences between Grade II and Grade III tumour categories were analysed with Mann–Whitney U test. According to the results, it was seen that radiomic features can be used to differentiate the features of tumour levels evaluated in the same category. These results show that by employing radiomic features brain cancer grade detection can help machine learning technologies and radiological analysis.

Keywords: Radiomics, glioma, image processing.

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1. Introduction

The use of artificial intelligence applications enables patients to be provided with faster and better healthcare. One of the diseases that causes the most deaths in the world is brain tumours. Brain tumours disrupt brain function and reduce the physical quality of patients, reducing their quality of life. The World Health Organisation (WHO) says that, the most common primary brain tumours are gliomas. The WHO identifies them in four ways according to their propagation tendencies. There are low grade glioma (LGG) and high grade glioma (HGG), among which are very low-grade (I), medium-grade (II, III) and high-grade (IV) [16]. Compared to gliomas in themselves, HGG glioblastomas are more complex and those with LGG are promptly treatable tumours. Those with HGG, that is class IV, spreads very quickly, but in other groups, this phenomenon is more stable and slow [23]. The evaluation of tumour grades is determined nowadays after histopathological examination. There areno clear parameters of mass lesions that predict tumour grade according to the radiological features. General information, such as the size and colour of the tumour, is insufficient to determine the grade of the tumour. Radiomics knowledge of the properties of the tumour can facilitate the decision to treat and acceleration of clinical procedures. Radiomics is a new area of quantitative imaging, creating a roadmap for the objective evaluation of the images of clinical cases using imaging features [14].

Radiomic features have an important place in many areas such as image processing, deep learning and machine learning. With the developing knowledge and technology, data scientists have developed important applications in areas such as image processing [24] and voice recognition [3]. The development of computer technology has provided quantitative features to be extracted from medical images. This new generation method, which is generally used to examine the images obtained in the medical field and to determine their grades, is called radiomics 0123[15] It is a new generation application that reveals comprehensive quantitative features of image data using radiomics feature extraction algorithms. The radiomics quantitative properties contain a number of significant prognostic data, with the inclusion of the molecular sub-properties of tumour images [1]. Semantic features are general tumour features that are visually evaluated by radiologists. These features do not reflect a common view, as they are intuitive and observational. Previously, single-sequence imaging was used in studies and was reasonably useful in producing a single feature. However, a single feature and a single sequence do not extensively contain all the features of gliomas. A multi-sequence MRI image is more effective in seeing various pathological degenerations of gliomas. Especially, the three-dimensional (3D) tumour image to be obtained within the scope of the study and the detection of its radiomic features will add a new dimension to the literature. In a study of brain tumours, the accuracy and reproducibility of feature extraction approaches were demonstrated to reveal the features of tumour shape and tissue information from MR images [36]. In another study conducted with breast MRI images, the features were extracted from the segmented images with the expectation maximisation algorithm and classified with the decision tree algorithm [25].

In this study, the effectiveness of radiomics data obtained from MRI image sequences of brain tumours in determining the grade of glioma was investigated. The tumour region was detected by the Grow Cut segmentation algorithm and a 3D image of the tumour was obtained. Radiomic features of the obtained 3Dtumour image were extracted with the 3D Slicer software. Spearman's correlation analysis and Mann–Whitney U test were used to find out which shape, first-order and tissue scale type are important in predicting the tumour grade in patient prognosis.

2. Material methods

2.1. Patient information

The patient MRI images used in this study were obtained from The Cancer Image Archive (TCIA), a large library of the National Cancer Institute, which provides data support in many studies around the

world. You can find detailed information about the data (http://cancerimagingarchive.net/) [8]. The data contained in TCIA, which is an open access library, provide information to researchers doing medical imaging studies in many areas [6].

All materials and images in the data set were used in accordance with all applicable laws, regulations and licensing policies regarding the protection of patient information in a great sensitivity in the study [2]. Each has a biopsy-proven Grade II and Grade III status. A total of 121 patient MRIs (77 Grade II and 44 Grade III) images were included in the study. Representative examples of Grade II MRI and Grade III MRI gliomas are shown in Figure 1 to illustrate the tumour appearances.
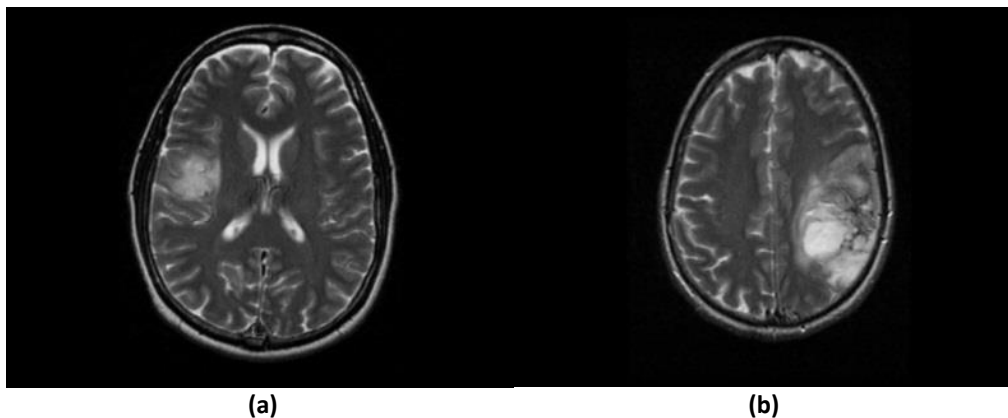

(a)   (b)

Figure 1. Gliomas of Grades II (a) and Grade III (b) on brain magnetic resonance images

2.2. Tumour segmentation

The most important basic function in the dataset is the determination of the region of interest (ROI) before the radiomic features are extracted. The tumour region, which is usually found in MRI, has a very small ratio compared to the background. This complicates the detection of Grade II and Grade III. For this purpose, the possible tumour region is taken into a convex area with ROI and this process is carried outmanually.

Higher success is achieved because the part outside the region is ignored. Many successful radiomic studies have used manual contour, but the perspective between users should be minimised. [7]. Although automated tools significantly affect the process of segmenting the ROI and reduces inter-user variability, it is not yet fully and efficiently available independent of radiologists. For this reason, segmentations created by experts should be tried together with different automatic segmentation tools and new algorithms should be developed. The effect of a single slice or features of the radiomics image obtained from a fixed size ROI varies greatly depending on the image feature [9].Therefore, more successful results can be obtained if the ROIs of all tumour slices are removed, not with a single slice of the image. For this purpose, 3D Slicer program was used in this study. This program, which has many features, is a free, public, comprehensive software package for image analysis, which can process many image data as well as MRI, which includes tools for image recording, radiomics feature extraction, segmentation and pre-processing. In the 3D slicer program, a 3Dtumour image was obtained by applying Grow Cut algorithm to each MRI. All segmentations of MRI were carried outon a NVIDIA GTX 1,050 graphics card with a 32GB RAM and a standard desktop computer.

2.3. Radiomics feature extraction

There are two types of features that can extract an image. These are general and local features. General features define the image as a whole, while local features define important points in the image [11].

It is quite difficult to determine the shape and tissue properties of tumour regions obtained from brain MRIs. These procedures have been found to be more accurate, feasible and reproducible with computational image extraction approaches [27]. Features extracted from the images can be categorised to advice radiologists and improve the diagnostic accuracy of tumour grades. In this study, a great number of radiomics features were analysed to estimate brain tumour grade, and these features were examined in three categories: morphological, first-order and texture features.

2.4. Morphological features

Morphological features, such as tumours' shapes, geometric features, margins and growth patterns, are the main components used in determining tumour grade levels. Fourteen global shape features were extracted from the enhancing lesion. These are features that aim to characterise the global structure of ROIs, such as the longest diameters of the shape such as volume, surface area, major and minor axis length, lengths of major minor axes and 3D and 2D tumour diameters.

2.5. First-order features

The first-order features, brightness, density and colour distribution of the tissues, reflect the properties of MRIs with tumours. The grey scale value distribution centre, which is one of these features, is a measure of the mean and variance of the distribution centre and the degree of increase in them. The skew reflects the balance between the two sides of the distribution and indicates whether the distribution is symmetrical. First-degree density properties were removed from 18 lesions. Among them, certain features were determined as well as basic features such as mean, median, minimum, distortion, energy, variance and homogeneity.

2.6. Textural features

Textural features are highly preferred in distinguishing tumour types. By looking at the textural features, bright compositions, such as whether the tissues in the tumour where the tumour is located or whether they are plain and understandable, can be determined easily, thanks to these features. Grey level coexistence matrix (GLCM), which is one of the most used matrix in this field, is known as a method that is very useful and gives an idea about the properties of image textures [21]. GLCM tumour radiomic features are used by many computer-aided systems. We extracted 24othertextural features from the enhancing lesion. Cluster shade, cluster prominence, contrast, entropy and energy are the main components that distinguish the most important tumour grades.

2.7. Statistical analysis

Statistical analysis is an important step in the examination of radiomic features. Therefore, the Statistical Package for the Social Sciences (SPSS) software, one of the most widely used programs in the world in terms of statistics, was used in the analysis of data. The Mann–Whitney U test was used to check the values of all radiomic features between Grade II and Grade III on the MRI. We selected radiomic features that showed significant differences between the grades (II and III) using SPSS tests. Relationships between the characteristics of each group were tested by Spearman's correlation analysis. In medical studies, the level of error is usually kept at the level of 0.05, so decisions are made with 95% confidence. *P* (probability) value is a value used to determine the presence of statistical significance [4]. In statistical tests, *p*<0.05 was considered statistically significant and it is possible to reduce the level of this error to 1%.

3. Results

Clinical and statistical significance differ from each other in medicine. Statistical significance is to make decisions or make predictions about the population of the same patients based on the sample of patients [14]. After the statistical significance is tested, clinical significance is discussed in order to decide the usefulness and usefulness of a finding that is significant. In order for a finding to be clinically significant, it should first be statistically significant [19].

In this study, statistical significance was primarily examined. Radiomics features of 121 patients, including Grade II (n = 77) and Grade III (n = 44), were obtained. A total of 56 features, namely first-order feature (n = 18), shape feature (n = 14) and texture feature (n = 24), have been removed.

3.1. Non-parametric test analysis

Non-parametric tests are used when data are not normal. When the distribution of the data was examined, it was seen that there was no normal distribution and the groups were not in equal numbers [10]. According to this information, non-parametric Mann–Whitney U test was used in the data set. Some first-order features of Grade II and Grade III tumour images are examined in Table 1.

Table 1. Mann–Whitney U test results of first-order radiomic features according to grade

	Energy	Entropy	Kurtosis	Maximum	Mean	Median	Minimum	Skewness	Variance
Mann–Whitney U	1,334.0	1,467.0	1,596.0	1,571.0	1,661.0	1,669.5	1,422.0	1,562.0	1,461.0
Asymp. Sig	0.049	0.221	0.597	0.507	0.859	0.895	0.143	0.477	0.209
Mean Rank Grade II	56.32	58.05	62.27	59.40	61.43	61.32	64.53	59.29	57.97
Mean Rank Grade III	69.18	66.16	58.77	63.80	60.25	60.44	54.82	64.00	66.30

According to Grade II and Grade III, there was no statistical significance between Grade II and Grade III in terms of other features except Energy. There was a significant difference between energy p = 0.049 and tumour grades. It was determined that mean and median values (p = 0.859 and p = 0.895) were quite high and there was no significant difference between these features and tumour grades. First-order features show that the energy feature creates a statistically significant difference between Grade II and Grade III. When the energy levels of the patients belonging to the Grade II group were examined, it was observed that the mean rank (56.32) was lower than the mean rank of the Grade III group (69.18). The skewness mean rank value was found to be significantly higher in Grade III tumours than Grade II tumours. As the tumour grade increases, the mean order value increases statistically.

Table 2. Mann–Whitney U test results of shape adiomic features according to grade

	Elongation	Least axis length	Maximum 2D diameter slice	Maximum 3D diameter	Mesh volume	Surface area	Voxel volume	Sphericity
Mann–Whitney U	1,628.0	883.0	941.5	910.0	864.0	774.0	859.0	945.0
Asymp. sig.	0.722	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Mean Rank Grade II	61.86	50.47	49.32	50.82	50.22	49.05	50.16	70.73
Mean Rank Grade III	59.50	79.43	81.43	78.82	79.86	89.01	79.88	43.98

When Table 2 is examined, there is a statistically significant between Grade II and Grade III according to morphological shape features in many features. ($p<0.005$). It was observed that there was a high level of statistically significant in 78.5% of total shape features, such as Least Axis length, Major Axis Length, Maximum 2DDiameter Row, Maxiumum2D Diameter Column, Maximum 2D Diameter Slice, Maximum 3D Diameter, Mesh volume, Minor Axis Length, Sphericity, Surface Area and Voxel Volume. This shows that morphological features have a very high effect in determining tumour

grades. When the MRIs of the patients were examined, it was seen that there was no significant difference in Elongation and Flatness features compared to Grade II and Grade III (p = 0.722 and p = 0.539). The highest difference between Grade II and III in terms of mean rank values was observed in the Surface Area.

Table 3. Mann–Whitney U test results of texture radiomic features according to grade

	Contrast	Correlation	Id_{mn}	Id_n	Cluster shape	Cluster tendency	Difference entropy	Difference variance	Sum squares
Mann–Whitney U	1,485.0	1,335.0	1,266.0	1,237.0	1,673.0	1,443.0	1,506.0	1,458.0	1,443.0
Asymp. sig.	0.260	0.053	0.021	0.014	0.910	0.176	0.311	0.204	0.176
Mean Rank Grade II	58.29	56.34	55.44	56.06	60.73	57.74	58.56	57.94	57.74
Mean Rank Grade III	65.75	69.16	70.73	71.39	61.48	66.70	65.27	66.36	66.70

When Table 3 is examined, there is a statistically significant difference between Grade II and Grade III levels in terms of GLCM texture radiomics features in some quality ($p<0.005$). There was a statistically significant between Grade II and Grade III in Id_{mn} (p = 0.021) and Id_n (p = 0.014) quality ($p<0.005$). There was no statistically significant (p = 0.910) difference between Grade II and III with cluster shape feature.

The significance values obtained are 0.276, 0.311 and 0.204 for Contrast, Difference Entropy, difference variance, respectively, and reject the hypothesis because they are greater than 5% significance value. Therefore, there is no statistically significant difference between the Contrast, Difference Entropy and difference variance features of Grade II and Grade III tumours.

3.2. Correlation test analysis

Correlation determines whether the linear relationship between two randomly selected variables in probability calculations and statistical data analysis is positive or negative and the strength of the relationship. In statistical use, correlation helps us determine how far the variables are from each other. The extremes of the dataset were checked before correlation analyses were performed. It was observed that there were no extreme values and the Spearman's test, which is a non-parametric correlation test, was applied to shape, first-order and texture groups.

Spearman's test was applied to the GLCM based on texture features vectors shown in Figure 2. Texture group GLCM radiomics features and the correlation between the features of the group were examined. When the GLCM-based texture radiomic features were examined, the correlation value between the contrast feature and the difference variance feature was found to be r = 0.996 and p = 0.001. This shows a very strong statistically positive relationship between these two features.
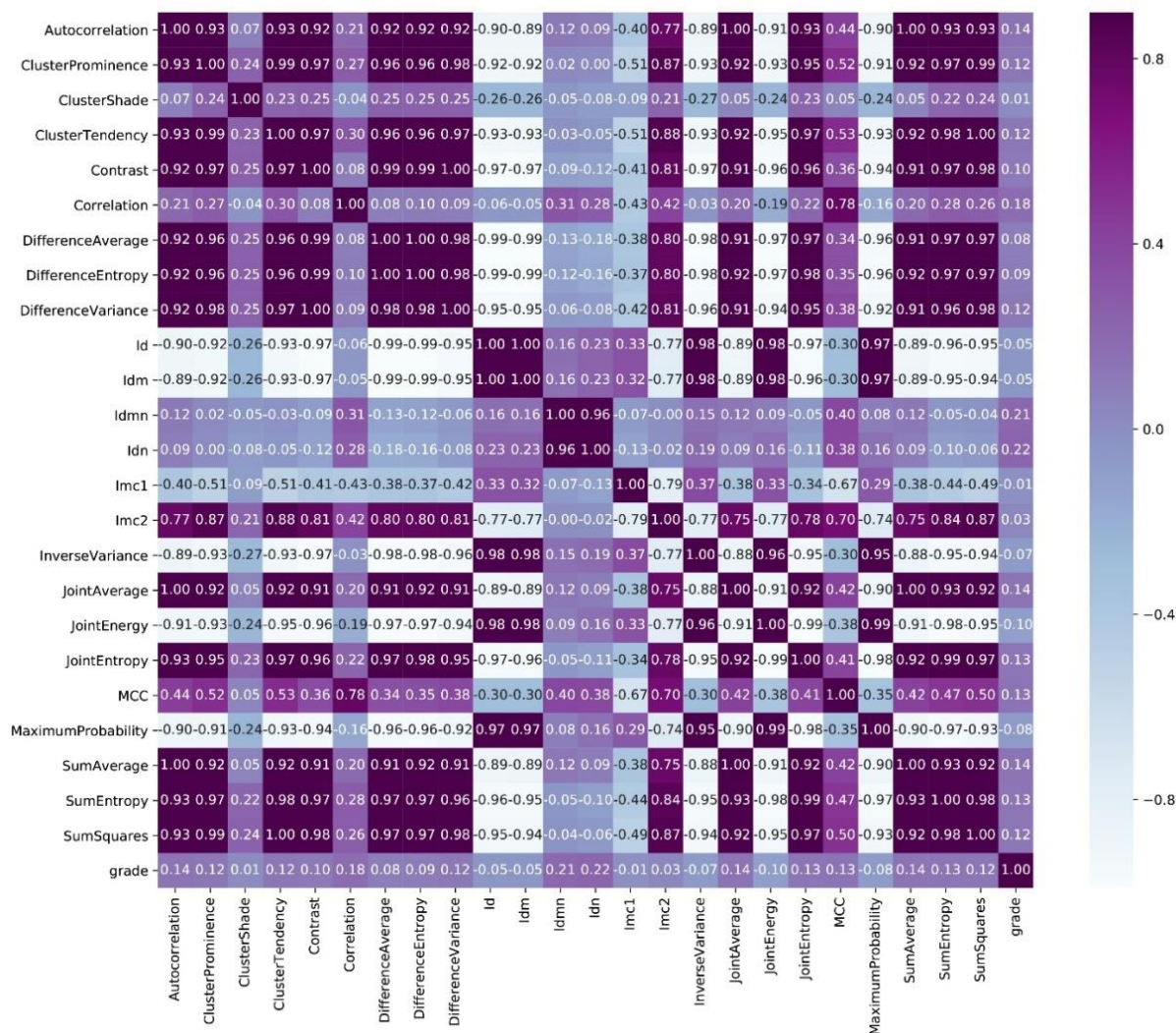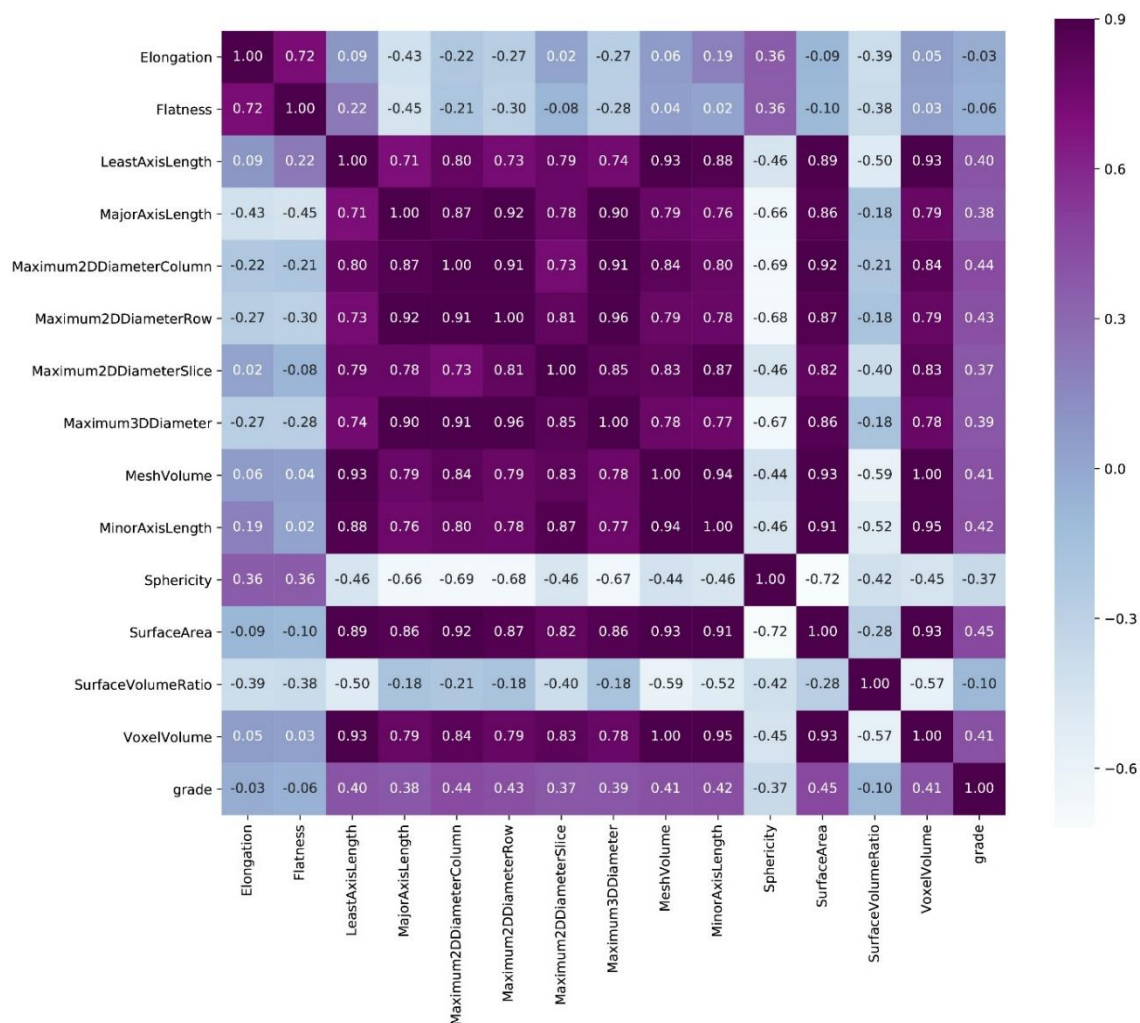
Figure 2. Spearman correlation results to texture features and grades

A very strong statistically significant relationship was found between contrast and difference-mean, since $r = 0.996$ and $p<0.001$. Contrast between IDM with $r = -0.969$ and $p<0.001$ is the negative direction and has a very strong statistical relationship.

Although there is a high correlation ($r = 0.96$) relationship between IDMN and IDN, the relationship levels with other features in both features are low. Correlation analysis was carried out within the group by applying Spearman's test to shape group radiomics features shown in Figure 3.

A statistically significant and strong relationship was observed between the surface area and voxel volume features, $r = 0.934$ and $p<0.001$, respectively. There is a strong negative statistical relationship between the surface area and sphericity, which is $r = -0.718$ and $p<0.001$, respectively, according to Spearman's test.

Figure 3. Spearman's correlation results to shape features and grades

When the elongation and flatness properties are examined, a positive and highly meaningful relationship is observed between them ($r = 0.719$; $p < 0.001$, respectively). The determination coefficient (r^2) between these two variables is 0.88. This finding is an indication that there is a common variance at the level of 88%. As the flatness increased, the elongation feature also increased statistically. On the other hand, a positive and low meaningful relationship was found between the degree and surface area ($r = 0.453$; $p < 0.001$). This shows that the main factor in grade is not statistically surface area. Apart from this, the highest semantic relationship with grade is between Maximum 2D Diameter Column after Surface Area, $r = 0.442$ and $p < 0.001$. There is a very low level semantic relationship between grade and sphericity, which is $r = -0.368$ and $p = 0.000$, respectively. Statistically, sphericity value increased as the grade level decreased. There is no significant correlation between mesh volume feature and elongation features. Spearman's correlation test was applied to the radiomics features of the first-order group, and the related features within the group were determined as shown in Figure 4.
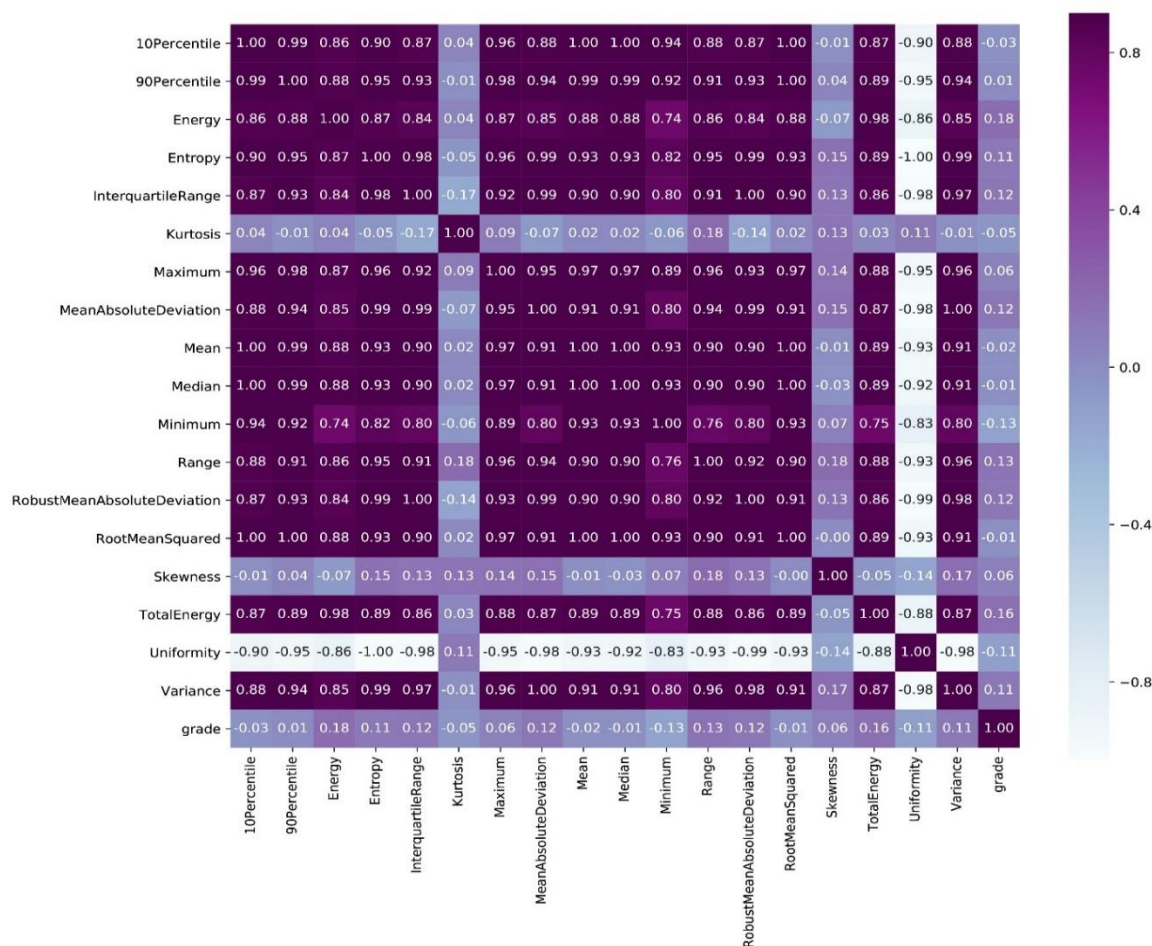
Figure 4. Spearman correlation results to first-order features and grades

The correlation value between energy and entropy properties is $r = 0.869$ and $p<0.001$, respectively, and there is a very strong statistically significant relationship. A strong negative statistical relationship between energy and uniformity is an important indicator with $r = −0,864$ and $p<0.001$. There was no statistically significant relationship between kurtosis and energy. Also, there was no statistically significant relationship between kurtosis and entropy. Range feature was found to have a strong statistically positive relationship with all other features except kurtosis and skewness. There was no significant relationship between skewness and interquartile feature, $r = 0.127$ and $p> 0.001$, respectively. Finally, there was no semantic relationship between grade level and first-order features.

4. Discussion

It is very difficult to determine Grade II and Grade III tumour levels by observing, and there are very few studies investigating the radiomic properties of these levels in the literature. The studies in the literature are generally carried out as LGG and HGG. The inability to analyse high and low grade correctly lies at the basis of misdiagnosis of glioma grades [20]. Using T1-weighted and diffusion-weighted imaging features, the meningioma and LGG were examined in a small sample set, but the small dataset limited the results [17]. Various radiomics features can be extracted from 2D or 3D tumour images depending on their size and shape.

The results showed that in 112 patients, the radiographic features (shape and texture) had high discriminating power in Grade II and Grade III of each MRI. There was a significant correlation

between entropy and energy from the first-order group. The extraction of quantitative features or parameters as a result of radiomics analysis makes this research area popular. Machine learning algorithms, statistical analysis and artificial intelligence applications [13] can determine thousands of abstract mathematical features that cannot be seen by the human eye [22]. Similarly, the GLCM-based properties were able to predict the systemic structures of GBM patients, such as difference entropy, correlation information measurement and inverse difference [5]. Another study showed that radiological properties (e.g., shape, signal density and tissue) obtained from GBM MRI can estimate the tumour [12]. In this study, it was seen that 14of these shapes, first-order and texture features were statistically significant in determining the Grade II and Grade III. Therefore, properties obtained from 3D tumour images can be used as an optimal radiomic feature for grade to gliomas in the medical field. [18] observed that the entropy value was significantly higher in HGG than LGG. Moreover, there is no statistically significant ($p = 0.221$) difference between Grade II and Grade III with entropy feature [18].

This study also has limitations that need to be addressed. First, the patient population consisted only of grades and it was quite difficult to examine similar level tumours. In addition, drawing ROIs by hand is a time=consuming process and constitutes the most important part of the studies. Automatic segmentation methods should be developed in this regard.

5. Conclusion

The subject of radiology is quite clear and realistically where by radiomic features will be used in medical studies in the future. It is inevitable to convert the image data obtained because of the radiological studies in the world to quantitative feature data. Technological infrastructures of research centres should be strengthened for these data to achieve high success in clinical settings with the developing computer algorithms. The blending of statistical analysis and images will pave the way for the development of new treatment methods in medicine. Statistical data obtained in this study will be useful in determining the method to be used in the detection and treatment of brain tumour types. The presence of radiologists, computer experts, statisticians and biomedical engineers in a multidisciplinary working environment will ensure successful results in this field.

6. Recommendations

Technological infrastructures of research centres should be strengthened for radiomic data to achieve high success in clinical environments by developing computer algorithms. The results obtained will provide a faster diagnosis to assist the specialists in the treatment of diseases. Especially, the findings obtained with the radiomic features and image processing methods of the levels of brain tumours contribute to the studies to be conducted in this field. The presence of radiologists, computer specialists, statisticians and biomedical engineers in multidisciplinary working environments will contribute greatly to the treatment of patients in the medical field.

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