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Diagnostic efficacy of computed tomography histogram analysis for the differentiation of histopathological low- and high-grade tumors in colorectal carcinoma

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ABSTRACT

Aim: Colorectal adenocarcinoma (CA) is the most common type of cancer worldwide and the third leading cause of cancer-related deaths. Primary pathological grade bears importance in the course of the disease. The possibility of non-invasive grading through radiology modalities is still an important issue. The present study aims to reveal whether a non-invasive grading similar to pathological grading can be performed using histogram analysis on computed tomography (CT) scan images.

Material and Method: 58 patients operated and diagnosed with CA pathologically were included in the present study. As for medical protocol, abdominal intravenous contrast CT scan images obtained from TOSHIBA Alexion and TOSHIBA Aquilion ONE (Toshiba Medical Systems, Nasu, Japan) devices with 120 kVp tube voltage were set to a window width of 400 and a window level of 40. Patient images from retrospective scanning were evaluated on a workstation. For the evalution of mass, intraluminal air, necrotic areas, pericolonic fat tissue or intra-mass large feeding vessels were not included in the measurement range. Mass size was measured on the largest axis according to the longest axis. For histogram analysis, regions of interest were positioned. Parameters included in the histogram analysis were pixels, mean, standard deviation, minimum, maximum, median, variance, entropy, size L%, size U%, size M%, kurtosis, skewness, uniformity, percent01, percent03, percent05, percent10, percent25, percent75, percent90, percent95, percent97 and percentile 99.

Results: Histogram analysis results obtained from three different measurements for each of 58 patients were not found to be statistically significant in the differentation of pathologically defined histological grading system.

Conclusion: Although the use of a non-invasive method instead of an invasive one may offer an advantage, was not statistically significant in the prediction of histological grade.

Keywords: Colorectal adenocarcinoma, histogram analysis, computed tomography, histological grade, texture analysis

INTRODUCTION

Colorectal cancer (CC) is the most common type of cancer worldwide (1). Grading in CC is closely related with tumor aggressiveness, survival and prognosis (2).

American Joint Committee on Cancer (AJCC) proposed a two-stage classification system, i.e. high and low grade, in order to standardize any potential subjectivity, reduce variations among different observers and increase its prognostic importance (3).

Tumor heterogeneity has been analyzed in many recent studies. It can be categorized into two groups as intertumor and intratumor heterogeneity (4).

Cellular heterogeneity observed in computed tomography (CT) scans often results from photon noise and obscures biological heterogeneity. Although routine CT scans may detect some distinguishing features of well or poorly differentitated tumors in preoperative staging in CC patients, they are still qualitative and subjective features, which may vary from one observer to another (5). A quantitative analysis of CT scans, however, is likely to reveal new promising biomarkers in the form of numerical parameters. If the clinical importance of these parameters is verified, they may significantly contribute to the redefinition of the role of diagnostic imaging and improvement of CC management.

Texture Analysis (histogram) analyzes the spatial distribution and relationship of pixels with different gray level values in an image for a more objective

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evaluation of tumor heterogeneity, thus offering a more unbiased interpretation of visual data in a gray region. Texture analysis includes statistical, model-based and transform-based methods. Arithmetic mean, standard deviation, variance and kurtosis are some histogram values that can be obtained from pixel values in a texture analysis (6). Texture analysis has been used in many individual treatment programs as an assisting method for patient management (7).

In today's world, the role of texture analysis in the diagnosis, treatment and monitoring of tumoral lesions has been analyzed, as manifested by some studies on its significance in lung cancer (8). As for CC, it was reported in the existing literature that measured values from primary lesion were independent predictors of 5-year survival and response to treatment (9). A pretreatment texture analysis in the presence of hepatic metastasis is correlated with pathological and clinical results (10). It was also reported that texture analysis was a potential biomarker for the evaluation of KRAS mutation (11) and a useful non-invasive method for rectal neuroendocrine tumor grading (12).

However, no studies have been so far carried out to analyze the relationship between texture analysis and histological grading of primary CC. The present study aims to analyze the potential diagnostic efficacy of CT histogram analysis for the differentiation of histopathological low- and high-grade tumors.

MATERIAL AND METHOD

The study was carried out with the permission of Kahramanmaraş Sütçü İmam University, Clinical Researches Ethics Committee (Date 2021/01 Decision No:12). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study design

The study was initiated with 154 patients who underwent colectomy between January 2009 and August 2019. 58 patients diagnosed with pathological colorectal carcinoma were included in the study. The patients who underwent preoperative chemo/radiotherapy were not included in the present study due to potential changes in their lesions. In addition, the patients without preoperative CT scans or a suitable CT scan protocol were also excluded from the study. Finally, the patients whose pathology in CT scans could not be optimally observed were also excluded. Their imaging archive records were analyzed in the study group. Demographical data such as sex and age and clinicopathological prognostic data were obtained from hospital records.

Pathological Diagnosis

Microscopic slides representing cancer tissue samples of the selected cases were analyzed by a pathologist again using NiKon Eclipse Ni light microscope. Histological grading was performed via a binary grading system suggested by WHO for colorectal tumor classification (Source: "WHO Classification of Tumors Editorial Board. WHO classification of tumors: digestive system tumours. 5th ed. Geneva: World Health Organization, 2019.") Cancer stage was determined using 8th edition of American Joint Committee on Cancer.

Accepted CT Scan Protocol, Image Processing and Analysis

Abdominal intravenous contrast CT scan images were obtained from TOSHIBA Alexion and TOSHIBA Aquilion ONE (Toshiba Medical Systems, Nasu, Japan) devices with 120 kVp tube voltage. Patient images were evaluated on a workstation on a 27-inch iMac computer (Apple Inc. Cupertino, California, USA), including the analysis of sagittal and coronal reformat images when necessary. Measurements for histogram analysis were made on the same computer with the Osirix program. Mass size was measured on the largest axis (axial, sagittal or coronal). Intraluminal air, necrotic areas, pericolonic fat tissue or intra-mass large feeding vessels were not included in the measurement range for the evalution of primary mass.

Regions of interest (ROI) were positioned and drawn manually for the histogram analysis. A circle corresponding to a diameter of 10 mm was taken as reference region for a standardized measurement. When the standardized circle was larger than the segment itself, an equal area (ellipsoid region) was taken as reference. Three measurements were performed on each lesion: proximal of small intestine, anal canal (distal end) and a medial point between these two ends. As a result, a total of 174 measurements (58 proximal, 58 medial and 58 distal) was obtained from 58 different patients. Histogram parameters were evaluated for three different measurements on each lesion to analyze their performances in the prediction of histological grade. Hounsfield unit (HU) value of each pixel in a ROI was transferred to an XML (eXtensible Markum Language) file. MATLAB version 2009b (MATrix LABoratory, Mathworks Inc., USA) was used to perform histogram analysis on XML files. The following parameters were used for histogram analysis: mean, standard deviation, minimum, maximum, median, variance, entropy, size L%, size U%, size M%, kurtosis, skewness, uniformity, percent01, percent03, percent05, percent10, percent25, percent75, percent90, percent95, percent97 and percentile99.

Statistical Analysis

The obtained results were analyzed using SPSS program ver. 22 (IBM corporation, Armonk, NY, USA). All values are presented in mean±SD. The normality distribution of the obtained data was analyzed using "Kolmogorov-Smirov Test". Normally distributed data were compared using Student T and ANOVA tests, while non-normally distributed data were compared using Mann-Whitney U and Kruskal-Wallis tests. The categorical values were given in % for descriptive data analysis. $p<0.05$ was accepted as the level of statistical significance.

RESULTS

While 17 patients (29.3%) were female, 41 patients (70.7%) were male. The age groups varied between 29 and 86. 22 patients (37.9%) were 65 or younger, whereas 36 patients (62%) were over 65.

The lesion was in the right colon in 24 patients (41.3%), left colon in 19 patients (32.7%) and in the rectum in 15 patients (25.8%). While the lesions were shorter than 5 cm in 26 patients (44.8%), they were 5 cm or longer in 32 patients (55.1%). The number of patients in T1, T2, T3 and T4 stages was 1 (1.7%), 7 (12%), 44 (75.8%) and 6 (10.3%), respectively. The number of patients in N0, N1 and N2 stages was 38 (65.5%), 13 (22.4%) and 7 (12%), respectively. 51 patients (%) were in M0 stage, while 7 patients (%) were M1a stage. The number of patients with conventional adenocarcinoma, mucinous carcinoma and signet ring cell carcinoma was 51 (87.9%), 5 (8.6%) and 2 (3.4%), respectively. In terms of histological grade, 44 patients (75.9%) had low-grade tumors, while 14 patients (24.1%) had high grade tumors. In all patients, the number of proximal, medial and distal lesion samples was 58 (33.3%), 58 (33.3%) and 58 (33.3%), respectively, reaching a total of 174 (%100) samples. None of 174 measured values from proximal (**Table 1**), medial (**Table 2**) and distal (**Table 3**) lesions of the patients were significantly correlated with 24 different histogram parameters.

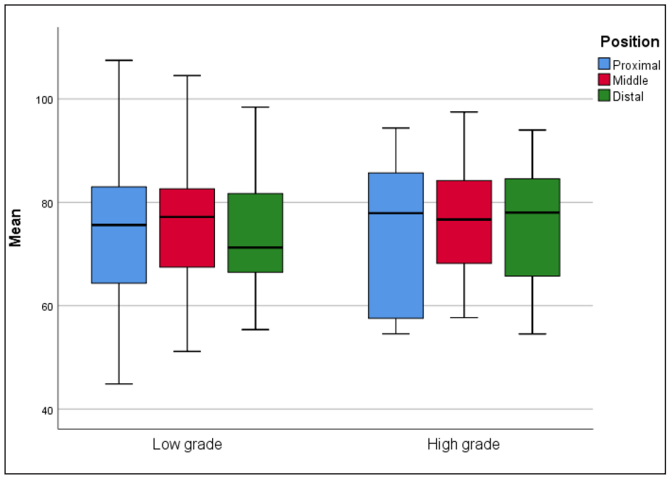

Figure 1. Distribution of histogram analysis

Table 1: Histogram analysis of the patients' primary proximal lesion measurements and their levels of statistical significance ($p<0.005$)

Histogram parameters	Low grade	High grade	p value
Mean	73.8235	74.204	0.929*
Standard deviation	32.05	21.5	0.042†
Minimum	28.68	32.07	0.513†
Maximum	126.36	117.14	0.504*
Median	74.102	74.214	0.979*
Variance	32.05	21.5	0.042†
Entropy	5.672	5.5828	0.286*
Size L%	29.39	29.81	0.928†
Size U%	15.7463	16.4517	0.303*
Size M%	30.66	25.86	0.304†
Kurtosis	29.57	29.29	0.957†
Skewness	29.93	28.14	0.73†
Uniformity	28.93	31.29	0.65†
Percent 01	28.56	32.71	0.451†
Percent 03	28.61	32.29	0.479†
Percent 05	41.9864	45.45	0.523*
Percent 10	48.7477	51.1357	0.621*
Percent 25	60.5114	62.0714	0.724*
Percent 75	87.1136	81.0714	0.812*
Percent 90	98.8273	96.6	0.644*
Percent 95	105.5057	102.7179	0.599*
Percent 97	109.4259	106.3593	0.581*
Percent 99	117.2755	112.752	0.441*

* Student T, †Mann-Whitney U

Table 2: Histogram analysis of the patients' primary medial lesion measurements and their levels of statistical significance ($p<0.005$)

Histogram parameters	Low grade	High grade	p value
Mean	75.6643	75.003	0.882*
Standard deviation	31.11	24.43	0.197†
Minimum	28.74	31.89	0.542†
Maximum	122.34	118.79	0.59*
Median	76.205	75.714	0.914*
Variance	31.11	24.43	0.197†
Entropy	5.6326	5.6167	0.837*
Size L%	29.42	29.75	0.949†
Size U%	15.7127	15.9178	0.82*
Size M%	29.72	28.82	0.863†
Kurtosis	29.28	30.18	0.863†
Skewness	29.68	28.93	0.884†
Uniformity	28.97	31.18	0.669†
Percent 01	28.41	32.93	0.383†
Percent 03	28.17	33.68	0.288†
Percent 05	42.6852	44.7	0.708*
Percent 10	50.4159	51.2714	0.87*
Percent 25	63.483	62.8036	0.879*
Percent 75	88.6364	87.2143	0.757*
Percent 90	99.3614	99.0857	0.957*
Percent 95	106.4193	104.075	0.666*
Percent 97	110.4441	107.8857	0.646*
Percent 99	118.2075	114.5857	0.554*

* Student T, †Mann-Whitney U

Table 3: Histogram analysis of the patients' primary distal lesion measurements and their levels of statistical significance (p<0.005)

Histogram parameters	Low grade	High grade	p value
Mean	74.1606	75.6012	0.716*
Standart deviation	30.39	26.71	0.479†
Minimum	28.41	32.93	0.383†
Maximum	119.34	116.14	0.572*
Median	74.909	75.75	0.837*
Variance	30.39	26.79	0.479†
Entropy	5.6416	5.6086	0.703*
Size L%	29.2	30.43	0.813†
Size U%	15.3822	16.1426	0.363*
Size M%	30.06	27.75	0.656†
Kurtosis	30.16	28.43	0.589†
Skewness	30.48	26.43	0.435†
Uniformity	28.28	32.71	0.414†
Percent 01	28.16	33.71	0.284†
Percent 03	28.18	33.64	0.292†
Percent 05	42.8318	46.0643	0.434*
Percent 10	49.8318	52.7643	0.505*
Percent 25	61.3409	63.5179	0.607*
Percent 75	86.9318	87.9643	0.799*
Percent 90	98.5455	98.4857	0.989*
Percent 95	105.0102	103.7679	0.793*
Percent 97	108.9134	107.2664	0.737*
Percent 99	116.03	112.7621	0.537*

* Student T, †Mann-Whitney U

DISCUSSION

The obtained data demonstrated that CT scan texture analysis results of primary CC were not correlated with histopathological grading. It can be clearly stated that homogenous or heterogeneous tumors did not correspond to high or low grade tumors from a histopathological perspective.

Blood flow heterogeneity in a tumor causes the formation of hypoxic zones, which may result in oxidative stress and genomic instability (13-15). Similarly, heterogeneous blood flow will deteriorate treatment response due to a low amount of chemotherapeutic agents transferred into areas with low vascularity.

Few studies have so far directly dealt with primary CC heterogeneity in the existing literature. Ganeshan et al. (16), which is one of these studies, suggested that primary tumors with a higher heterogeneity were correlated with a poor prognosis and survival and that such an inversely proportional correlation was likely to be related with high cellular density and vascular permeability (8). It was also argued in the same study that contrast CT scan results were likely to be correlated with vascular permeability of a tumor and, as a result, tumors with a higher vascular permeability would lead to a lower contrast resolution and less heterogeneity in texture analysis. This argument is based on the idea that aggressive high-grade tumors display a more homogeneous structure. Another study on the histogram analysis of non-contrast CT scans in 17 patients with small cell lung cancer indicated a negative correlation between homogeneity and tumor stage (16).

Previous studies have underlined the importance of heterogeneity and homogeneity for tumor structure. However, there are multi-centered and multiple variables in such studies which result from differences in the analysis environment (histological type and grade of primary pathology), pathogenesis (hypoxia, vascularity etc.) and obtained results (prognosis, stage, survival etc.). Although the present study paid utmost attention to the selection of patients and image analysis, the above-mentioned differences and various limitations led to analysis results which contradict with those reported in the current literature, thus requiring a multi-dimensional analysis method for the research topic in question. The specification of these difference in future studies on this topic and emphasis on the limitations listed below will yield more reliable and valid results.

Reaching satisfactory historical grading results using a preoperative non-invasive method in CC patients will contribute to the diagnosis of potentially risky stage 2 cancer patients who can benefit from additional adjuvant and neoadjuvant treatments. In addition, it will also guide post-treatment process and facilitate the optimization of cancer treatment based on prognostic factors during a period with variable and unpredictable prognosis.

Since histological grading is an invasive procedure with inconsistent results for different observers, similar to the present study, future studies on the prediction of tumor grade using texture analysis are likely to replace virtual biopsy and eliminate contradicting observation results.

Given that CC patients usually suffer from moderately differentitated adenocarcinoma, texture analysis may increase existing characterization and emerge as a promising and additional prognostic biomarker for tumor staging.

Limitations

Firstly, limited sampling from certain areas on tumoral tissues, uncertainties regarding the similarity of texture analysis regions on these tissues and insufficient size of ROI can be considered as various histopathological limitations in the present study. Secondly, the results of this retrospective study were obtained from a single patient population. Thirdly, although our CT scan images were obtained in portal venous phase in order to minimize contrast differences, it cannot be

said to eliminate heterogeneity in imaging parameters completely. Fourthly, ROI positioning was carried out by a single user, which makes it difficult to make multi-centered and variable generalizations based on the obtained results. In order to reduce observer bias and variability caused by ROI positioning in texture analysis, further studies are needed for the analysis of multiple readers and test-retest reliability. Fifthly, the characteristic ratio of (nearly 3/1) low grade and high grade patients in our analysis is likely to have affected our results negatively. A study on a group of patients in similar numbers may yield more reliable results.

CONCLUSION

The view that CT scan tissue analysis can be applied to individualized treatment plans as a non-invasive and quantitative method for preoperatively distinguishing low-grade and high-grade CA patients is still only a possibility. Further studies are required to improve texture analysis for neoadjuvant treatment in rectal cancer patients with a high risk of local recurrence and for adjuvant treatment in high risk stage 2 colon cancer patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kahramanmaraş Sütçü İmam University, Clinical Researches Ethics Committee (Date 2021/01 Decision No:12)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients**.**

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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